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Clinical impact of the methodological quality of fetal doppler standards in the management of fetal growth restriction

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CLINICAL IMPACT OF THE METHODOLOGICAL QUALITY OF FETAL DOPPLER STANDARDS IN THE MANAGEMENT OF FETAL GROWTH RESTRICTION

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HACE CONSTAR:

Que el trabajo de investigación titulado “Clinical impact of the methodological quality of fetal Doppler standards in the management of fetal growth restriction” que presenta Sara Ruiz Martinez, Licenciada en Medicina para optar al GRADO DE DOCTOR, fue realizado bajo mi dirección, no existiendo impedimento alguno para su defensa como compendio de publicaciones.

Y para que conste a los efectos oportunos firmo el presente en Zaragoza a 16 de Septiembre de 2019

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La presente Tesis Doctoral ha sido estructurada siguiendo las directrices de la normativa para la presentación de tesis doctorales como compendio de artículos, con mención de Tesis internacional, aprobada por la comisión de Doctorado de la Universidad de Zaragoza el día 17 de noviembre de 2008.

Los estudios que conforman esta Tesis Doctoral pertenecen a la misma línea de investigación. Los resultados obtenidos gracias a la realización de estos estudios, han aportado información relevante y novedosa sobre el tema y han sido recogidos en cuatro artículos originales, publicados en diferentes revistas de amplia difusión internacional:

1. **Ruiz-Martinez S**, Volpe, S. Vannuccini, A. Cavallaro, L. Impey, C. Ioannou. An objective scoring method to evaluate image quality of middle cerebral artery Doppler. J Matern Fetal Neonatal Med. 2018 Jun 27:1-181. doi: 10.1080/14767058.2018.1494711

   Estado: Publicado
   Factor de impacto: 1.569
   Tercer cuartil

2. Oros D, S, **Ruiz-Martinez S**, Staines-Urias E, Conde-Agudelo A, Villar J, Fabre E, Papageorghiou AT. Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio: a systematic review. Ultrasound Obstet Gynecol. 2019 Apr;53(4):454-464. doi: 10.1002/uog.20102

   Estado: Publicado
   Factor de impacto: 5.595
   Primer decil

3. **Ruiz-Martinez S**, Papageorghiou AT, Staines-Urias E, Villar J, Gonzalez de Agüero R, Oros D. Clinical impact of Doppler reference charts to manage foetal growth restriction: the need for standardisation. Ultrasound Obstet Gynecol. 2019 Jun 25. doi: 10.1002/uog.20380.

   Estado: Publicado
   Factor de impacto: 5.595
   Primer decil

4. **Ruiz-Martinez S**, Oros D. Re: ISUOG Practice Guidelines on ultrasound assessment of fetal biometry and growth: Time to pay attention to bias in Doppler studies. Ultrasound Obstet Gynecol. 2019 Sep;54(3):419. doi: 10.1002/uog.20405.

   Estado: Publicado
   Factor de impacto: 5.595
   Primer decil

5. **Ruiz-Martinez S**, Staines-Urias E, Abadia N, Conde-Agudelo A, Villar J, Delgado JL, Burgos J, Stirnemann J, Parra-Cordero M, Arduini D, Acharya G, Paules C, Papageorghiou AT, Oros D and the FETHUS Consortium. International prescriptive fetal brain Doppler standards (FETHUS project): study protocol

   Estado: En revisión en BMJ Open
   Factor de impacto: 2.376
   Segundo cuartil

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1.ABREVIATIONS

AC	Abdominal circumference
ACM	Arteria cerebral media
AEDF	Absence end diastolic flow
AGA	Adequate gestational age
ALARA	As low as reasonably achievable
APO	Adverse perinatal outcomes
AU	Arteria Umbilical
BPD	Biparietal diameter
CI	Confident interval
CPR	Cerebroplacental ratio
CRL	Crown rump length
EB	Exceed of bases
EFW	Estimated fetal weight
FHR	Fetal heat rate
FL	Femur length
FRG	Fetal growth restriction
FVW	Flow velocity waves
GWG	Gestational weight gain
HC	Head circumference
ICC	Interclass correlation coefficient
IUGR	Intrauterine growth restriction
LMP	Last menstrual period
MCA	Middle cerebral artery
NT	Nuchal translucency

PI	Pulsatility index
PRISMA	Preferred Reporting Items for Systematic Reviews
RCP	Ratio cerebroplacentario
RI	Resistance index
S/D	Systolic/diastolic ratio
SD	Standard deviation
SGA	Small for gestational age
US	Ultrasound
UA	Umbilical artery

2. INTRODUCTION

2.1. Ultrasound and Doppler

- **Physical bases of ultrasound and Doppler**

Ultrasound (US) was born after the sinking of TITANIC in 1912, due to the need to find submerged objects. The tragedy of TITANIC inspired British scientist L. F Richardson to describe the possibility of detecting iceberg by ultrasound. (1)

After that, with ultrasound technologies, during the Second World War the SONAR (figure1) (sound navigation and ranging) was developed, contributing to the location of objects in the sea (2).

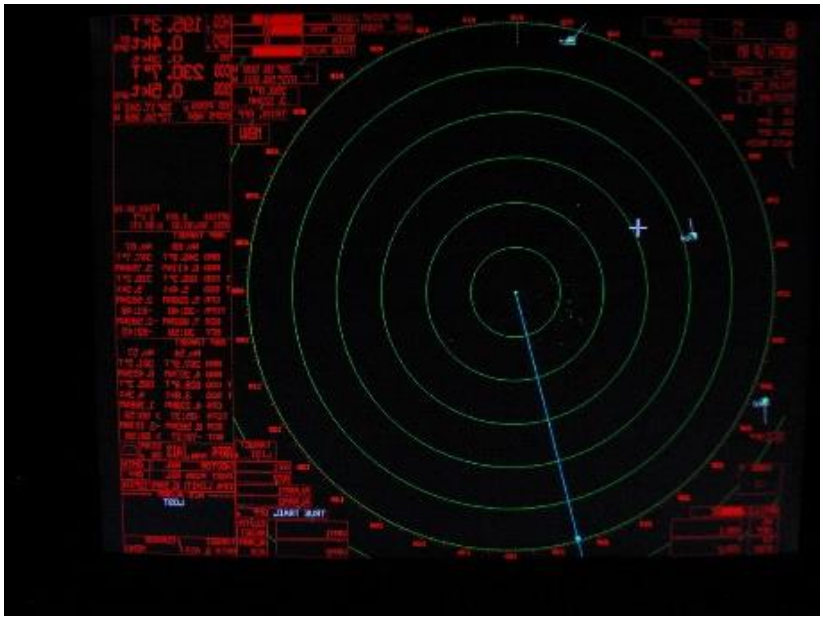


Figure 1: SONAR, used during Second World War

After the war Dr. Douglas Howry applied this technology, military until that moment, in the field of medicine(3). It was not until 1973, with the arrival of the grayscale image, that the use of ultrasound with its B mode was disseminated using the medical diagnosis differentiating structures.(4) Thanks to computer advances, gray-scale and real-time ultrasound was developed. Subsequently, other applications such as Color Doppler or Power Doppler have appeared.

Ultrasound, by definition has a frequency greater than 20,000 Hz, impossible to detect by the human ear. Medical images use frequency ranges between 3 and 15 MHz (5). The figure below shows frequency ranges of sounds from ultrasound to infrasound detected by animals. Between them there are sounds audible for humans (20Hz-20KHz).

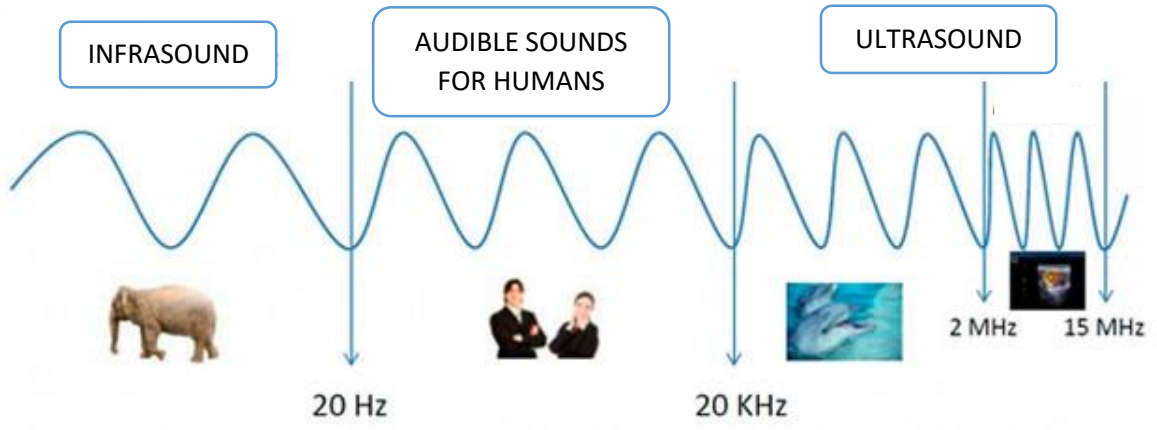


Figure 2: Frequency ranges of sounds

Echoes, on the other hand, are sounds that are reflected or bounced when they hit a surface or barrier. Between two contiguous means of different acoustic impedance there is an interface, defined as the surface capable of reflecting sounds or ultrasound. The greater the difference in acoustic impedance between them, the greater the intensity of the echo. In echography this impedance is reflect by the echogenicity, with different grey scale. In the human body from highest (hyperecochoic) to lowest impedance (anechoic) we find: bone, muscle, water and air (6). The figure 3 shows different echogenicity in echography:

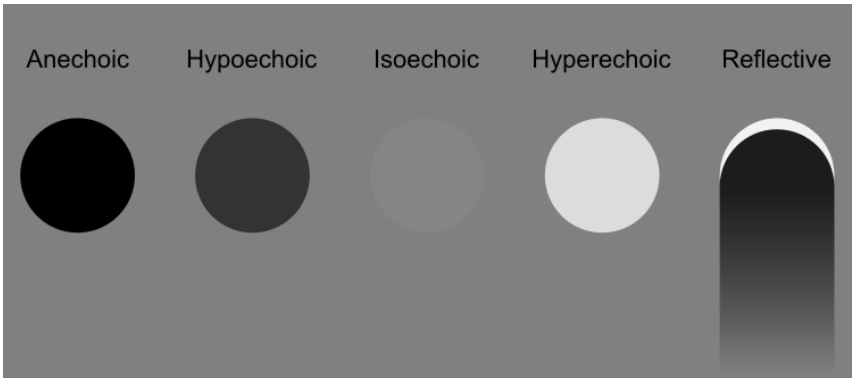


Figure 3. Echogenicity scale in echography

The Doppler effect (figure 4) was described by the Austrian physicist Christian Doppler, in the year 1845 and describes the change in frequency that is observed when there is movement between the sending and receiving source. This frequency difference is called the doppler frequency. (7) In the blood vessels, the movement of the blood flow can be observed, by approaching or moving away from the ultrasound probe the red blood cells (figure 5)

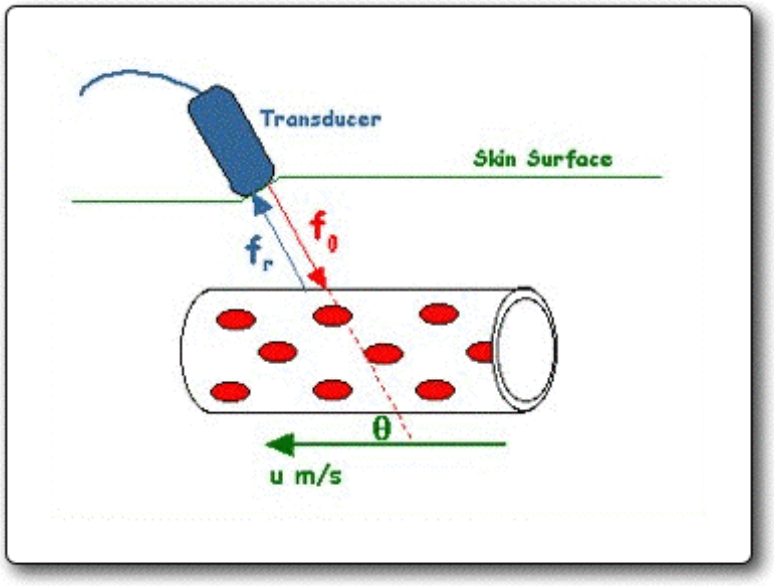


Figure 4: Doppler effect.

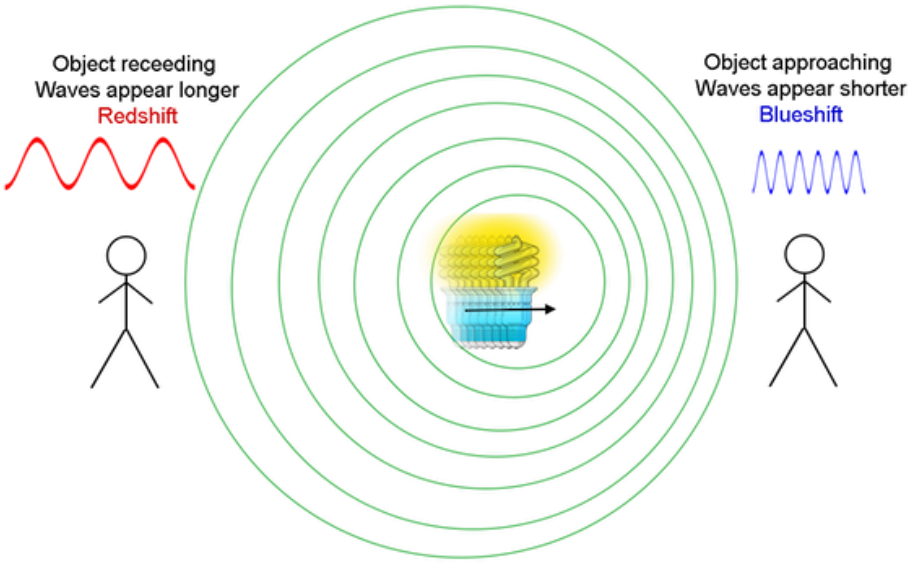


Figure 5: In echography, with Doppler colour it is possible to differentiate the flow direction.

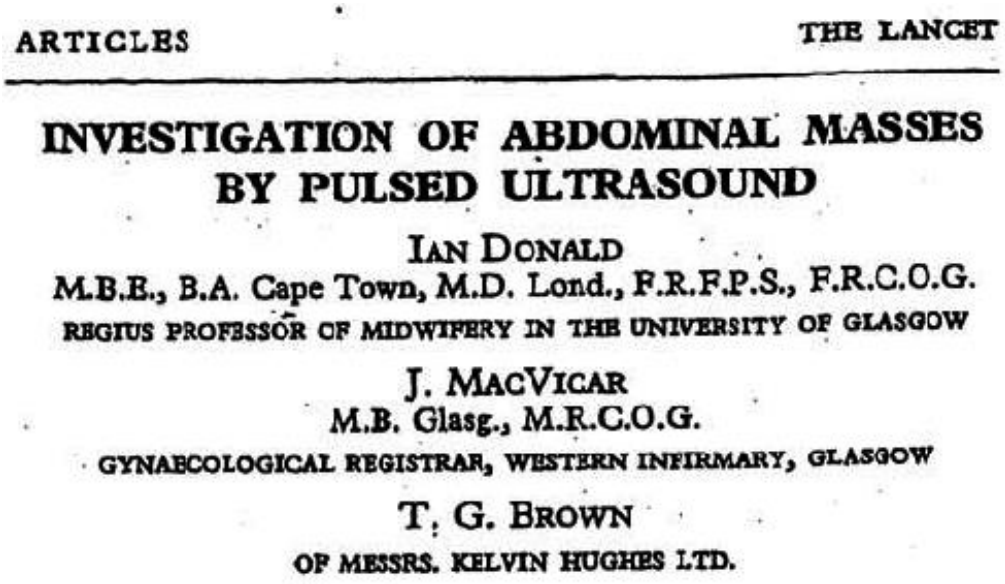
The obtained doppler signal can be represented in 3 modes: as an audio signal, a colour signal or by means of a graphic representation (pulsed doppler). It is in this graphic representation that the spectrum of frequencies detected as a function of time and speed of the red blood cells is shown. And this is the most used mode in obstetrics for the study of fetal vascularization.(8)

- **Ultrasound and doppler applies to medicine**

In the 1950s, the US is accepted by medical societies as a diagnostic instrument in medicine, awakening the interest of research groups. (9) The first article published in a prestigious scientific journal, was in Lancet, in 1958, where the experience was described in a group of 100 normal patients with abdominal pathology(10), and many today consider Donald Ian as the pioneer of ultrasound (figure 6).

In the 1970s with the arrival of the gray scale, the first images of human anatomy were obtained by differentiating the different tissues and, at the end of that decade, the first real-time images of high resolution were obtained.(9)

The first applications of ultrasound in medical diagnosis were made by neurologists, managing to suspect the presence of occupations in one of the cerebral hemispheres. Subsequently, gynecologists began exploring the intrauterine fetal anatomy using the two-dimensional, non-grayscale B mode. Almost simultaneously, cardiologists begin to use M-shaped ultrasound to study the heart, both in its structure and function. The first teams of Eco-Doppler, in the hands of vascular surgeons, begin to allow listening and studying in curves, the frequency changes produced by arterial and venous flows. (11)



ARTICLES THE LANCET

INVESTIGATION OF ABDOMINAL MASSES BY PULSED ULTRASOUND

IAN DONALD
M.B.E., B.A. Cape Town, M.D. Lond., F.R.F.P.S., F.R.C.O.G.
REGIUS PROFESSOR OF MIDWIFERY IN THE UNIVERSITY OF GLASGOW

J. MACVICAR
M.B. Glasg., M.R.C.O.G.
GYNAECOLOGICAL REGISTRAR, WESTERN INFIRMARY, GLASGOW

T. G. BROWN
OF MESSRS. KELVIN HUGHES LTD.

Figure 6: First publication about ultrasound in medicine

- **Ultrasound and doppler in fetal medicine**

The diagnostic tool par excellence in obstetrics is fetal ultrasound, it is the technique that collects the ultrasound emitted by the probe that passes through the uterus turning these electrical impulses into images of the grayscale fetal anatomy according to the impedance of the different fetal tissues (figure 7). Ultrasound, as long as it is used in a reasonable manner minimizing the exposure time to reduce possible thermal effects, will be considered a safe technique. So far there is no evidence that the use of diagnostic ultrasound is related to fetal structural alterations, low birth weight, tumour lesions or language changes, among others. For this reason, it should always be used under the motto ALARA (11)

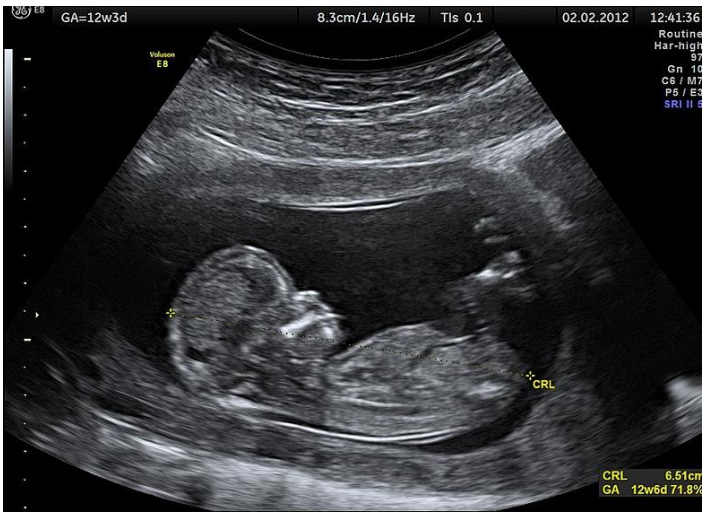


Figure 7: Example of echography in first trimester of gestation

The use of Doppler ultrasound to investigate the pattern of waveforms in the umbilical artery (UA) during pregnancy was first reported in 1977(12).Since then, ultrasound technology has developed further and much more complex assessment of fetal circulation has become standard clinical practice in obstetrics units worldwide. Doppler assessment of fetal well-being in high-risk pregnancies improves several clinical outcomes and reduces the risk of perinatal deaths and may result in fewer obstetric interventions(13). However, existing literature does not provide conclusive evidence about its benefit as a screening tool in all pregnancies.(14)

Different Doppler modalities (figure 8) are used in obstetrics: continuous-wave, pulsed-wave, colour and power Doppler flow(15). While colour and power Doppler provide visualisation of the blood flow and its direction, pulsed Doppler allows reproducible measurements of the blood velocities. The measurements obtained will reflect, in any vessel studied, the cardiac contraction force, density of the blood, vessel wall elasticity, but more importantly peripheral and downstream resistance(16)

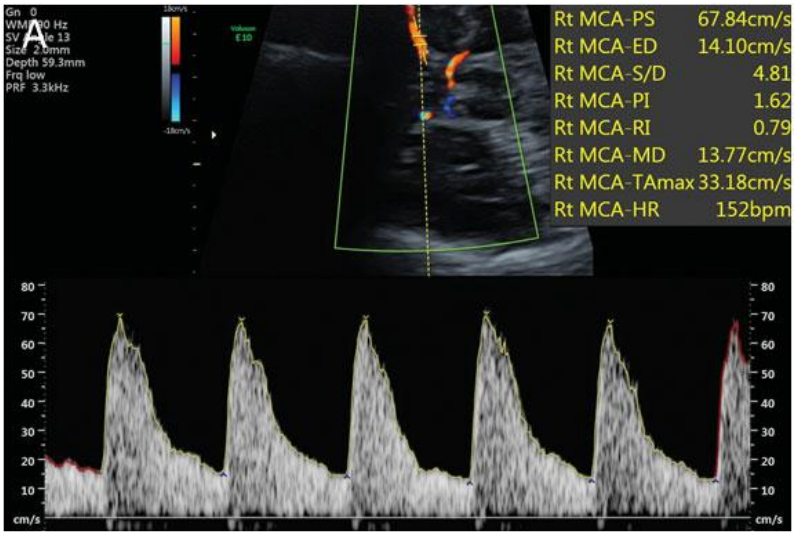


Figure 8: Example of fetal Doppler (MCA Doppler index)

2.2 Fetal growth restriction

Fetal growth restriction (FGR) appears when the fetus does not reach its biological growth potential as a consequence of impaired placental function, which may be because of a variety of factors.

There is great controversy in the definition of FGR. Classically, the fetus has been defined as a fetus with an estimated fetal weight (EFW) below the 10th percentile in the absence of morphological abnormalities or alterations of the fetal doppler. (17) . Differentiating like this, the small fetuses of low risk with those fetuses with greater risk of adverse perinatal outcomes (APO)

Recently, in 2016 a consensus of experts was published that redefined the concept of FGR (table 1) to be able to better select fetuses at risk of APO (18) , as shown in the following table, and always in the absence of morphological or genetic abnormalities:

Early FGR (<32weeks)	**AC/EFW <3rd centile or AU-AEDF Or** 1. AC/EFW<10 th centile with 2. UtA-PI>95th centile and/or 3. UA-PI >95th centile
Late FGR (>32 weeks)	**AC/EFW <3rd centile** **Or at least two out of three of the following** 1. AC/EFW<10 th centile 2. AC/EFW crossing centiles> 2 quartiles on growth centiles 3. CPR<5th centile or UA-PI>95th centile

Table 1: Current definition of IUGR(18)

- **Short and long term complication of FGR**

FGR fetuses have a higher risk of mortality and morbidity in the short and long term(19). On the one hand, the probability of intrauterine mortality and adverse perinatal outcomes such as neonatal acidosis, lower Apgar score or higher number of cesarean sections due to fetal acidosis have increased. The FRG neonates are prone to acquire separate complications after birth. A few of these complications include perinatal asphyxia, meconium aspiration, persistent pulmonary hypertension, hypothermia, hypoglycemia, hyperglycemia, hypocalcemia, polycythemia, jaundice, feeding difficulties, feed intolerance, necrotizing enterocolitis, late-onset sepsis, pulmonary hemorrhage(20) (table 2).

In addition, on many occasions the termination of pregnancy is necessary prematurely due to the high risk of intrauterine death, causing iatrogenic prematurity with all the consequences and complications of fetal immaturity that this can entail.

On the other hand, there are also medium and long term consequences. Numerous studies describe neurocognitive development disorders in SGA fetuses with cerebral redistribution during the fetal stage (21). It has been observed worse neurocognitive development in these children in early childhood such as lower scores on cognitive testing, difficulties in schools or require special education, gross motor and minor neurologic dysfunction, behavioral problems (attention deficit hyperactivity syndrome) growth failure, etc.(22) (table 2).

Already in 1920 Baker observed that children born with low weight had a higher incidence of coronary heart disease, diabetes mellitus, hyperinsulinemia and hypercholesterolemia (table 2). This association has been confirmed over the years with different studies although the causes are not clear that there are numerous hypotheses, the theory of "fetal programming" is one of the strongest currently and argues that there are intrauterine epigenetic changes in fetuses with FGR that would favor the development of these diseases. (20)

More recent studies confirm this increased risk of endocrine and cardiovascular diseases in adulthood in fetuses with FGR (18)

FETAL/NEONATAL COMPLICATIONS	CHILDHOOD AND ADULTHOOD COMPLICATIONS
Intrauterine fetal death	Growth retardation
Meconium aspiration	Behavioural problems (attention deficit hyperactivity syndrome/autism
Perinatal asphyxia	Minor neurological dysfunction
Hypo/hyperglucemia	School education difficulties/need for special education
Hypocalcemia	Low cognitive/ intelligence score
Hypotermia	Poor academic performance
Necrotizing Enterocolitis	Poor strenght and work capacity
Polycitemia/Hyperviscosity	Poor visuo-motor perception and motor incompetence
Inmunodeficiency	Poor social competence
Low serum ferritin	Cerebral plasticity
Pulmonary haemorrhage	Major/minor motor incompetence
Persistent pulmonary hypertension (PPHN)	Hypercholesterolemia
Renal dysfunction	Coronary heart disease
Retinopathy of premature	Diabetes mellitus

Table 2: Neonatal complication vs childhood and adulthood complications

- **Hemodynamic aspects of the fetus and its alteration in FGR**

Placental insufficiency translates into two main pathologies that are usually related although they can manifest separately, preeclampsia and restricted intrauterine growth. The final cause of this placental insufficiency is still unknown but we do know how the hemodynamic alteration sequence appears in the FGR, and this is what we use for the control and monitoring of these fetuses.

First of all, when there is anomalous placentation (figure 9), the uterine arteries have a vasoconstriction that translates into an increased risk of developing these pathologies, preeclampsia and FGR. Although it is not necessary to objectify this alteration to diagnose a FGR fetus. (23)

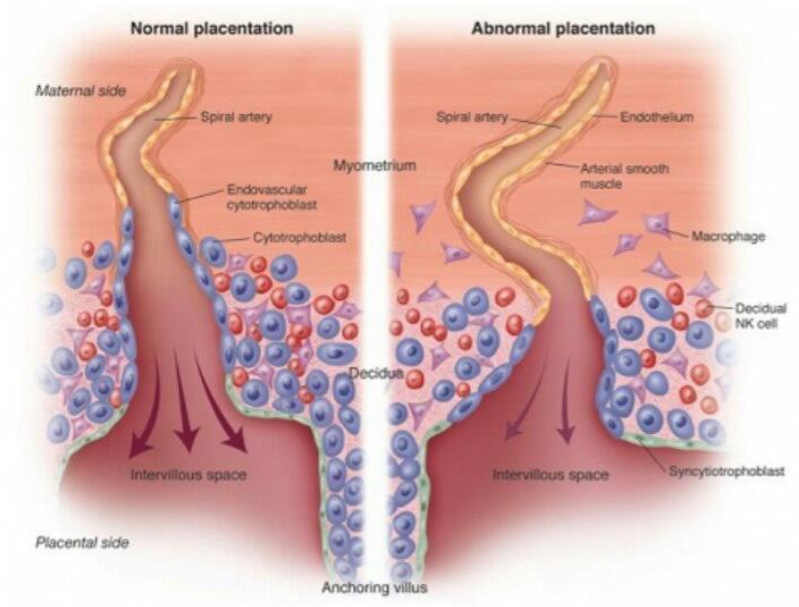


Figure 9: Vasoconstriction of spiral artery in abnormal placentation

Once a SGA fetus is diagnosed, with the EFW(24), an exhaustive evaluation of the fetal Doppler must be performed. When the Doppler vascularization begins to alter, a vasoconstriction of the umbilical artery is observed as a result of a possible placental insufficiency. In response to this incident, the fetus responds with a vasodilation of the blood vessels that risk the vital organs, and a decrease in resistance in the middle cerebral artery is objectified. This sequence, which tries to preserve blood flow in the main vital organs, has been called brain sparing, described few decades ago(25). Doppler abnormalities in the umbilical artery (UA) are related closely to placental

insufficiency(26), whilst changes in the fetal middle cerebral artery (MCA) reflect fetal cardiovascular adaptations to hypoxia or blood flow redistribution to protect the fetal brain.

As for ultrasound effects, once the wave is obtained, different measures can be calculated that can be quantitative, such as maximum speed, semi-quantitative such as pulsatility or resistance indices, or qualitative such as flow direction.

The case of the peak of systolic velocity of the MCA, as a quantitative change is used for the diagnosis of fetal anemia in its different scenarios such as anti-D isoimmunization. (27) Although it has also been studied as a marker to predict fetal death in FGR fetuses.(28)

In extreme circumstances, qualitative changes, such as the absence of diastole or reversal of end-diastolic velocity (figure 10), have been widely studied and are related to hemodynamic instability and adverse perinatal outcomes (29), clearly indicates an increased risk of fetal demise(30).

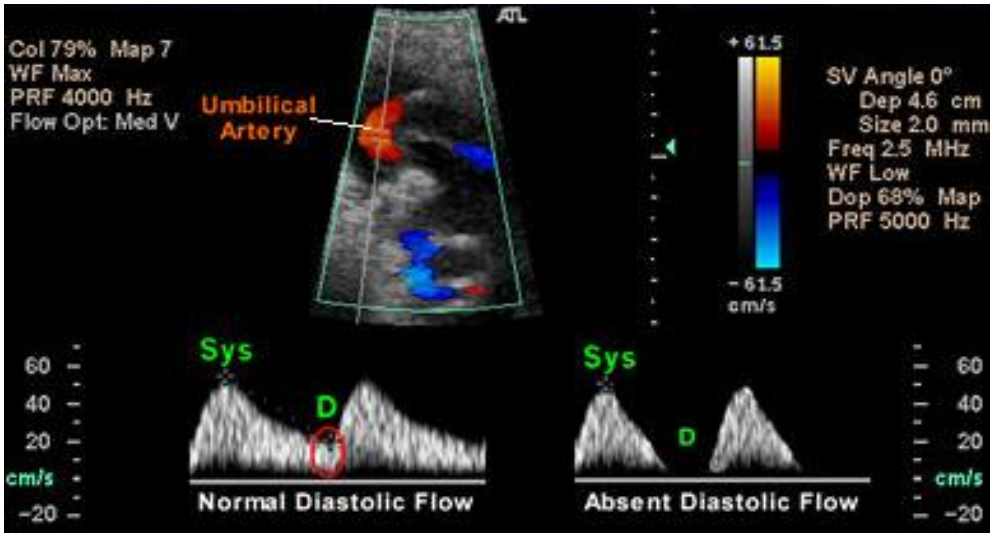


Figure 10: Normal and absent diastolic flow

Therefore, if we identify these changes, it seems reasonable to end the pregnancy due to the risk of intrauterine fetal death. (31)

Since, when qualitative changes appear, it is usually too late to intervene and improve the outcomes, we need tools that allow us to get ahead of that moment with the aim to end the pregnancy in the best possible conditions.(17,32)

For this reason, we can observe semiquantitative changes, that is, the pulsatility and resistance indexes that we can calculate when we obtain the Doppler wave, these parameters are the most often quantified to assess FGR(33). The most commonly used in clinical practice is the pulsatility index that is calculated with the following formula: (34) (figure 11)

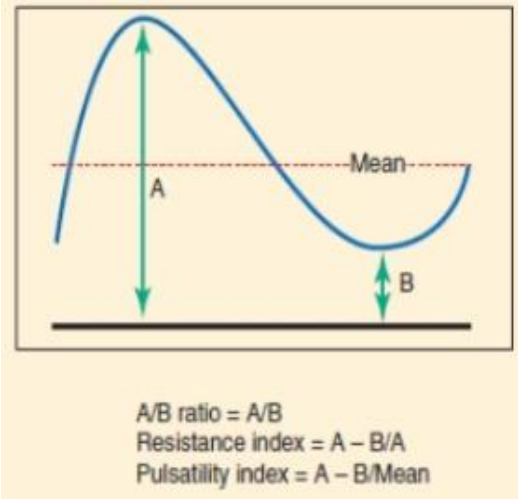


Figure 11: PI = (peak systolic flow - peak diastolic flow) / (mean flow)

These indexes reflect the vascular resistance by quantifying the differences between the peak systolic and the end- diastolic velocity within blood vessels of interest in each cardiac cycle(35). A high ratio in umbilical artery indicates a high vascular impedance and possible feto-placental compromise. In extreme circumstance the blood flow at the end of diastole may be absent or even reversed (qualitative changes).

In the intrauterine growth restriction (IUGR) fetus, when fetal hemodynamics begins to alter, a series of semiquantitatives changes appear, usually consecutive but not in all cases. An increase in the pulsatility index (>95th centile) in the umbilical artery and a decrease of PI in the middle cerebral artery (<5th centile) are observed, as well as a decrease in the cerebroplacental ratio (<5th centile).(36)

These alterations are usually progressive. First, quantitative changes appear in these pulsatility and resistance indices and subsequently, qualitative changes in the wave graphs.(37)

Cerebroplacental ratio (CPR) is calculated by dividing the Doppler index (pulsatility index (PI), resistance index (RI), or systolic/diastolic ratio (S/D)) of the MCA by that of the UA. Physiologically, CPR represents the interaction of alterations in blood flow to the brain, as manifest by increased diastolic flow as a result of cerebrovascular dilatation due to hypoxia and increased placental resistance, leading to decreased diastolic flow in the UA(38). The cerebroplacental ratio (CPR), has been shown to be more sensitive to hypoxia than its individual components in animal and clinical models(39)(40), and more recent work has suggested that CPR, is an independent predictor of fetal compromise(41), Cesarean section (42,43) and adverse perinatal outcome (39,44–46)
Therefore, UA and MCA Doppler indices and CPR are currently used to modify the scheduling of antepartum surveillance and, in some cases, to time delivery of the compromised fetus (26,41)
The association between cerebral redistribution and the worst perinatal and neurological development suggests the existence of some degree of fetal injury in the early stages of hemodynamic adaptation to hypoxia in FGR and even varies according to the gestational weight of the foetuses (21,47,48)

2.3. Methodology and biases in clinical research

The success of an intervention is based on obtaining quality information; that obtained from previous experiences and studies are likely to have been influenced to a greater or lesser extent by possible errors(49).

These errors can originate randomly, by chance (random errors); or in a systematic way, impacting on the accuracy, or on the veracity of the results of the study. The systematic error, also called bias, is of great importance because it affects the internal validity of a study, invalidating the results of the investigation. Unlike the random error, the systematic error is not compensated by increasing the sample size (Casal & Mateu, 2003)

It is essential to know the possible segos to avoid them and that the results obtained are of high quality (50).

In clinical research and more specifically in obstetrics, we can identify different types of biases. As stated in the editorial of Sotiriadis et al(51), the different studies on Doppler and their reference values are subject to different types of biases at level of studies such as:

- Expectation bias: clinical examiners subconsciously regress their measurements closer to the expected range
- Verification bias: when the confirmation of a diagnosis after a test differs systematically depending on the results of the test
- Recall bias o memory effect: occurs when the examiner reevaluates the same image or test and remembers the previous result of the same
- Hawthorne effect: refers to the improvement of the results when the subjects are aware that they participate in an investigation study, this entails results that are too ideal and not representative of reality

On the other hand, Sotiriadis et al described differents types of cognitive bias:

- Anchoring bias: it is about clinging to the initial impression and not adjusting it according to the information that is obtained
- Satisfaction of search bias: occurs when the examiner stops searching for abnormalities once a diagnosis has been reached.
- Framing bias: This is strongly influenced by subtle ways in which the problem is worded, or 'framed', preventing the addition of relevant information if the desired option is not among the possible predetermined ones when collecting the study data.
- Attribution bias It refers to classifying a subject in a category for various reasons before having the results of the study, by background, social class or others.
- Availability bias: occurs when a diagnostic assumption is made based on the ease with which relevant information comes to mind

- Hindsight bias. This refers to the tendency to overestimate the predictability of an event after the event is known or to interpret a result afterwards when we already know the result
- Fatigue: errors that occur after a day's work due to the examiner's own fatigue

In obstetrics, as in any clinical investigation, it is essential to know the possible biases to avoid them and to be able to carry out studies of high methodological quality whose results can be extrapolated to any population of similar characteristics.

Due to the great importance of methodological quality in research studies, numerous working groups, such as the MOOSE group, have published recommendations (52) and check list, i.e. PRISMA(53), to facilitate this work. If clinical studies follow these recommendations, the probability of biases will decrease and we will obtain quality results that can be extrapolated to any population.

2.4. Standardization of measurements and reference values in fetal medicine

In fetal medicine, it is essential to work with standardized measures and universally validated reference values, obtained from studies of high methodological quality.

Depending on the ultrasound results obtained and their interpretation as pathological or not, important clinical decisions are going to be made, such as terminating the pregnancy prematurely or continuing with the risks involved in either decision.

There are different studies that analyze the methodological quality of the reference values of different ultrasound parameters. This is the case of the study conducted by Napolitano et al. (54) in which a systematic review of the reference charts used for the measurement of CRL and its correlation with gestational age is performed , this fact is essential to date a pregnancy capable of making decisions based on of fetal maturity attributed to each week of pregnancy. In this review, 29 studies were evaluated in full text and 29 criteria of methodological quality were used giving a score to each of the

studies. In addition, they analysed, together, the percentage of studies that met each of the quality criteria. Finally, they concluded that there is great variability in the way CRL is measured and, consequently, great heterogeneity in the ultrasound dating of pregnancy.

On the other hand, there are several studies that analyze how to take measurements of fetal biometrics, reaching an international consensus and standardizing the way of measuring the fetal head, abdomen or femur (55). Then, applying a mathematical formula and thus obtaining an estimated fetal weight (24). To interpret this EFW it is essential to have fetal growth charts that fit the population and give us a reliable diagnosis of SGA foetuses, and with this propose. In recent years, several systematic reviews have been carried out to assess the quality of the reference values used in clinical practice. Eighty-three studies of 32 countries describing fetal weight reference values have assessed by Ioannou et al (56), they used 23 quality criteria for transversal studies and 24 for longitudinal studies, and analysed the percentage of studies met these criteria and, finally, the authors demonstrated great heterogeneity between the studies assessed recommending strict criteria of methodological quality to create reference chart for fetal size.

In the same way, the review of Ohadike et al(57) evaluated the methodology of the studies that describe the reference charts for optimal gestational weight gain (GWG), concluding that the poor quality of the studies would justify the variability of obstetric management in clinical practice.

After several publications about the poor quality of fetal growth charts, some authors have tried to create the appropriate fetal growth standards (58,59). The most important group in this area is INTERGROWTH-21$_{st}$ with some studies about international estimated fetal weight standards(60).

Regarding fetal doppler, numerous guidelines describe how to obtained the measurements of pulsatility index UA and MCA(61) and different studies give normal values of fetal doppler, for example, one of the most used chart is that of Arduini et al

(62) published in 1990. But, on the contrary, so far the quality of these studies has not been analyzed and has not been verified that these Doppler reference charts are reliable and of high methodological quality that can be extrapolated to the general population.

2.5. Relevance and justification of the research study

Doppler velocimetry is used to assess small-for gestational- age (SGA) fetuses at risk of adverse perinatal outcome.

The measurement of Doppler must follow standards so that the values obtained are adequate and reproducible in order to maximize the potential of Doppler assessment in clinical practice.

Therefore, high quality images are essential for the evaluation of fetal Doppler. Guidelines describe the correct Doppler assessment but there are no published studies objectively assessing its key criteria and no scoring method for assessing whether an MCA Doppler image has been recorded accurately.

Patterns of Doppler progression have been characterized clearly and it has been reported that qualitative changes in UA Doppler, such as the presence, absence or reversal of end-diastolic velocity, clearly indicates an increased risk of fetal demise. However, the association between quantitative changes in UA and MCA Doppler, as measured using PI, and perinatal and long-term outcomes has not been clearly established. As a result, multiple reference ranges for fetal doppler have been reported. This lack of evidence may be explained, at least, by the quality methodology used to establish these values and this fact could have important implications for clinical practice.

Given the importance and consequences of managing the fetus with restricted intrauterine growth, it is important to use objective criteria to obtain measurements of the MCA Doppler from high quality images as well as universal reference values from high-quality studies.

El Doppler fetal se utiliza para evaluar fetos pequeños para la edad gestacional (PEG) con riesgo de resultado perinatal adverso.

Para que los valores obtenidos sean adecuados y reproducibles, la medición de Doppler debe estar estandarizada y así, maximizar su potencial en la evaluación de estos fetos en la práctica clínica.

Por ello, es esencial obtener imágenes ecográficas de alta calidad. Las guías clínicas describen la forma correcta del medir el Doppler, pero no existen estudios publicados que evalúen objetivamente sus criterios de calidad ni establecen sistemas de puntuación para evaluar si una imagen Doppler se ha obtenido correctamente.

La secuencia de progresión del Doppler fetal ha sido descrita claramente y hay evidencia de que los cambios cualitativos en el Doppler de la arterial umbilical (AU), como la presencia, ausencia o inversión del flujo diastólico, indican un mayor riesgo de muerte fetal. Sin embargo, la asociación entre los cambios cuantitativos en el Doppler de AU y ACM, medidos con el índice de pulsatilidad (IP), y los resultados perinatales y a largo plazo no se han establecido claramente. Como consecuencia, se han publicado multitud de valores de referencia del IP del Doppler fetal. Esta falta de evidencia podría explicarse, al menos parcialmente, por la calidad metodología utilizada para establecer estos valores y este hecho podría tener importantes implicaciones para la práctica clínica.

Dada la importancia y consecuencias que tiene el manejo del feto con crecimiento intrauterino restringido, es importante utilizar criterios objetivos para obtener mediciones del Doppler fetal a partir de imágenes de alta calidad, así como, valores de referencia universales procedentes de estudios de alta calidad.

3. HYPOTHESIS

MAIN HYPOTESIS

- The methodological quality of fetal doppler image acquisition as well as of normal doppler references ranges entails a significant impact on the clinical management of fetal growth restriction.

SECONDARY HYPOTESIS

- The use of an objective quality scoring system in the acquisition of doppler images could improve the accuracy and reproducibility of fetal Doppler measurements.

- There is a great heterogeneity between the published fetal Doppler reference values. These differences could be partially explained by methodological biases of the studies.

- The differences between the cut-off values of normal Doppler reference ranges would have important implications in the clinical management of fetal growth restriction

HIPOTESIS PRINCIPAL

- La calidad metodológica de la adquisición de imágenes de Doppler fetal, así como de los valores de referencia Doppler, tiene un impacto significativo en el manejo clínico de los fetos con crecimiento intrautero restringido.

HIPOTESIS SECUNDARIAS

- El uso de un sistema de puntuación de calidad objetivo en la adquisición de imágenes Doppler podría mejorar la precisión y la reproducibilidad de las mediciones de Doppler fetal.

- Existe una gran heterogeneidad entre los valores de referencia de Doppler fetal publicados. Estas diferencias podrían explicarse parcialmente por sesgos metodológicos en los estudios.

- Las diferencias entre los puntos de corte de los valores de referencia Doppler tendrían implicaciones importantes en el manejo clínico de los fetos con crecimiento intrautero restringido.

4. OBJECTIVES

MAIN OBJECTIVE

- To assess the clinical impact of the methodological quality of fetal Doppler reference ranges in the management of fetal growth restriction.

SECONDARY OBJECTIVE

- To validate an objective scoring system of quality for middle cerebral artery pulsed wave Doppler images.

- To assess methodological quality of all published studies reporting reference ranges for umbilical artery and fetal middle cerebral artery Doppler indices and cerebroplacental ratio.

- To assess clinical variability in the management of fetal growth restriction according to published fetal Doppler reference values.

- To raise awareness in the scientific community of the need to create universal and prospective reference values of fetal Doppler for the management of IUGR fetuses.

- To propose a study to develop methodologically robust Doppler reference standards according to a set of quality recommendations, for practical clinical applications as an international benchmark for the assessment of fetal brain Doppler.

OBJETIVO PRINCIPAL

- Evaluar el impacto clínico de la calidad metodológica de los valores de referencia de Doppler fetal en el manejo de la restricción del crecimiento fetal.

OBJETIVOS SECUNDARIOS

- Validar un sistema de puntuación objetivo de calidad para imágenes de Doppler en la arteria cerebral media.

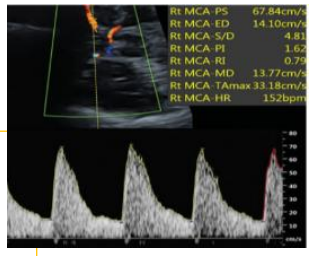
- Evaluar la calidad metodológica de todos los estudios publicados que establecen rangos de referencia para los índices Doppler de la arteria umbilical, la arteria cerebral media fetal y el índice cerebroplacentario.

- Evaluar la variabilidad clínica en el manejo de la restricción del crecimiento fetal de acuerdo con los valores de referencia Doppler fetales publicados.

- Concienciar a la comunidad científica de la necesidad de crear valores de referencia universales y prospectivos de Doppler fetal para el manejo de fetos CIR.

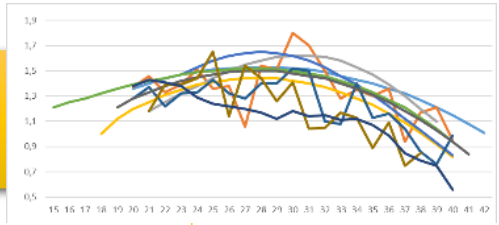
- Proponer un estudio para desarrollar valores de referencia Doppler metodológicamente sólidos de acuerdo con un conjunto de recomendaciones de calidad, aplicables a la práctica clínica como referencia internacional para la evaluación del Doppler cerebral fetal.

5. PROJECT SUMMARY



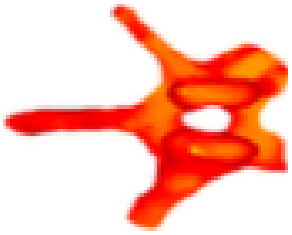
Project 1: Image quality

- An objective scoring method to evaluate image quality of middle cerebral artery Doppler



Project 2: Methodology quality and clinical impact

- Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio
- Clinical impact of Doppler reference charts to manage foetal growth restriction.



Project 3: Doppler standarization

- Time to pay attention to bias in Doppler studies.
- FETHUS PROJECT: Fetal Haemodynamic Ultrasound Standards.

5.1. PROJECT 1: AN OBJECTIVE SCORING METHOD TO EVALUATE IMAGE QUALITY OF MIDDLE CEREBRAL ARTERY DOPPLER

To avoid biases when establishing universal reference values in any field, it is essential to start from a solid base of high quality. Therefore, in the fetal Doppler, it is very important to obtain correct ultrasound images, which meet strict quality criteria to make correct measurements that finally give us universal reference values. Measuring the middle cerebral artery is not easy, special conditions must be met that largely depend on the sonographer who performs the test, although there are other conditions such as maternal breathing or fetal movement, sometimes, uncontrollable. Therefore, it is essential to perform these measurements with an excellent ultrasound technique and, in addition, carry out strict quality controls to minimize biases as much as possible.

This study aims to validate an objective scoring system for middle cerebral artery (MCA) pulsed wave Doppler images to ensure high quality images and measurements.

In addition to being published in an impact journal, this study was presented as oral communication at an international congress.

Ruiz-Martinez S, Volpe, S. Vannuccini, A. Cavallaro, L. Impey, C. Ioannou. An objective scoring method to evaluate image quality of middle cerebral artery Doppler. J Matern Fetal Neonatal Med. 2018 Jun 27:1-181. doi: 10.1080/14767058.2018.1494711

Estado: Publicado

Factor de impacto: 1.49

Cuarto cuartil

Oral presentation: An objective system to evaluate the quality of Middle Cerebral Artery Doppler images in the session. 27th World Congress on Ultrasound in Obstetrics and Gynecology. September 2017, Vienna (Austria)

a. MATERIAL AND METHODS

This study was carried out entirely at the University of Oxford, with data from healthy population patients at John Radcliffe Hospital.

All pregnant women in the John Radcliffe Hospital, Oxford, United Kingdom are offered MCA Doppler assessment as part of routine growth scan at 36-week gestation.

Sample: Around 1270 examinations were performed between December 2016 and January 2017 and a random 10% sample was selected. According to a previously published (63) power calculation, a sample of 125 examinations is adequate to detect a 10% difference between two reviewers with 90% power, assuming a rate of interobserver agreement of 80%. The current study is covered by ethics reference REC 17/SC/0374 granted on 27 July 2017; patient informed consent is not required as this is a retrospective review of routinely collected data.

***Study design*:** All images were taken by four different trained sonographers, following the same institutional protocol and using two different machines (Phillips Epiq 7 and GE Voluson E8). An objective scoring system was developed based on the ISUOG Practice Guidelines (61). The following six criteria (Table 3) were defined: anatomical site, magnification, image clarity, angle of insonation, sweep speed adjustment, and velocity scale and baseline adjustment. Once these features are fulfilled, the pulsatility index, resistance index, and peak systolic velocity are obtained automatically from at least three uniform waves.

Two assessors were blinded to each other's rating results and they rated all images subjectively as "acceptable" or "unacceptable." To assess the images objectively, the same two assessors used the 6-point image scoring system (table 3). One point was awarded for each criterion satisfied; and zero if the criterion was not satisfied (figure 12). All criteria were accorded equal weight and the sum of points was the final score. We considered images scoring four or more points as good quality; and those scoring less than four points as poor quality.

Criterion	Description
Anatomical site	Axial brain section visualizing the thalami and sphenoid wings and identifying the circle of Willis by colour Doppler with the gate placed in the proximal third of the MCA
Magnification	MCA image occupies at least 50% of the screen
Image clarity	Waveform should be clear without artefacts and tracing should be accurate
Angle of insonation	Less than 15º followed by angle correction as close as possible to 0º
Sweep speed adjustment	3-10 waveforms are visualised
Velocity scale and baseline adjustment	Waveforms occupy 75% of the screen

Table 3. Image scoring criteria for MCA Doppler Image

b. STATISTICAL ANALYSIS

Score distributions were compared between the two observers using the Wilcoxon test. Subjective and objective agreement between observers was assessed using the unadjusted (Cohen) and the prevalence adjusted and bias-adjusted (PABAK) Kappa statistics(64). Interitem consistency of the six criteria of the scoring system was assessed for each observer using the Cronbach's alpha statistic (65). Analyses were performed using IBM SPSS statistics version 23.

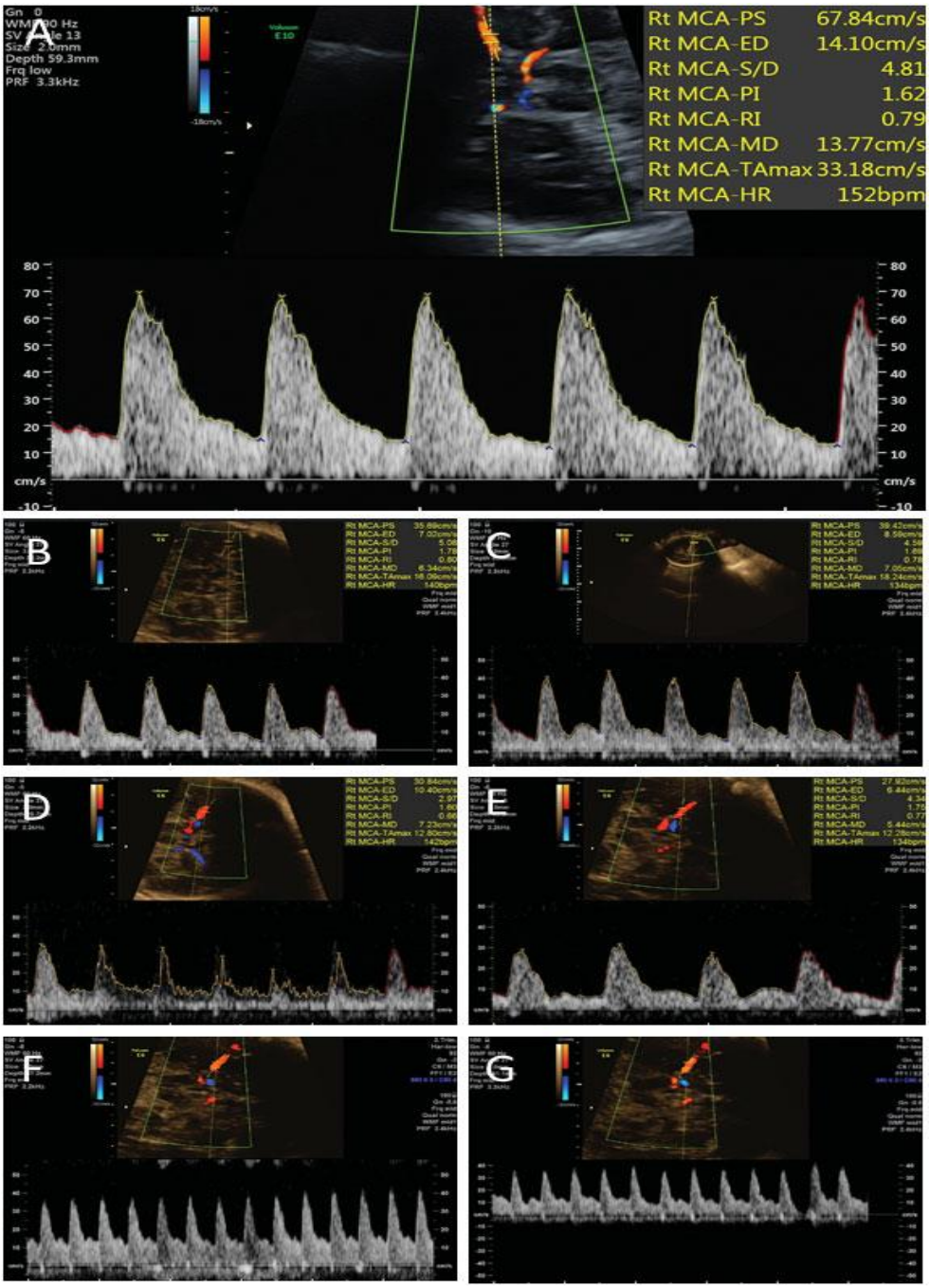


Figure 12 : Representative examples of middle cerebral artery (MCA) images (A) where all scoring criteria are met; (B) wrong anatomical site: circle of Willis and MCA poorly identified with gate too lateral and near the skull; (C) inadequate magnification; (D) suboptimal image clarity resulting in inaccurate tracing of the waveform; (E) no angle correction; (F) no sweep speed adjustment resulting in too many waves per image; and (G) no baseline and velocity scale adjustment so that waveform does not fill up the screen

c. RESULTS

A total of 124 middle cerebral artery Doppler images from 4 sonographers were used. Using subjective scoring, reviewers A and B judged 71 (57.3%) and 79 (63.7%) images respectively to be acceptable. 60 (48.4%) images were acceptable by both assessors whereas 34 (27.4%) were unacceptable by both, an agreement rate of 75.8%.

The distribution of objective scores amongst subjectively rated images is shown in Table 4.

	Objective image score					
Subjective assessment	**1**	**2**	**3**	**4**	**5**	**6**
Unacceptable A	1 (1.9%)	11 (20.8%)	15 (28.3%)	15 (28.3%)	10 (18.9%)	1 (1.9%)
Acceptable A	-	-	3 (4.2%)	26 (36.6%)	32 (45.1%)	10 (14.1%)
Unacceptable B	2 (4.4%)	7 (15.6%)	16 (35.6%)	13 (28.9%)	6 (13.3%)	1 (2.2%)
Acceptable B	-	-	5 (6.3%)	21 (26.6%)	37 (46.8%)	16 (20.3%)
Unacceptable by both A and B (Objective score A)	1 (2.9%)	11 (32.4%)	10 (29.4%)	10 (29.4%)	2 (5.9%)	-
Unacceptable by both A and B (Objective score B)	2 (5.9%)	7 (20.6%)	13 (38.2%)	8 (23.5%)	3 (8.8%)	1 (2.9%)
Acceptable by both A and B (Objective score A)	-	-	1 (1.7%)	20 (33.3%)	29 (48.3%)	10 (16.7%)
Acceptable by both A and B (Objective score B)	-	-	1 (1.7%)	17 (28.3%)	28 (46.7%)	14 (23.3%)

Table 4: Comparison between subjective assessment and objective scoring for both observers

Images deemed subjectively acceptable would unsurprisingly have an objective score most often 4-6 and never 1-2. Conversely images deemed unacceptable would usually have an objective score 1-3, but it is interesting to note that 10-20% of those images could have an objective score of 4-6.

Criterion	Agreement (%)	Kappa Cohen (95% CI)	Adjusted Kappa PABAK (95% CI)
Subjective A / Subjective B	75.8	0.496 (0.341 – 0.651)	0.516 (0.365 – 0.667)
Subjective A / Objective B	78.2	0.493 (0.334 – 0.652)	0.565 (0.419 – 0.710)
Objective A / Subjective B	75.0	0.460 (0.311 – 0.609)	0.500 (0.348 – 0.652)
Subjective A / Objective A	79.8	0.530 (0.375 – 0.685)	0.597 (0.456 – 0.738)
Subjective B / Objective B	76.6	0.494 (0.347 – 0.641)	0.532 (0.383 – 0.681)
Objective A / Objective B	91.9	0.780 (0.651 – 0.909)	0.839 (0.743 – 0.935)

Table 5: Agreement between subjective assessment and objective scoring for MCA Doppler image

Using the objective scoring method the agreement rate between reviewers increased to 91.9%, adjusted k = 0.839 compared to subjective rating agreement 75.8%, adjusted k = 0.516 (Table 5). Both reviewers had a median score of 4 (range 1-6) and the score distributions are shown in Figure 2. Reviewer A had a mean score 4.27 whereas reviewer B a mean score 4.17 and this small difference was statistically significant (Wilcoxon signed rank P = 0.022). Table 3 demonstrates that objective assessment of the image quality using the overall image score has the highest reliability between the two reviewers when compared to any other combination of assessment methods.

Criterion	Agreement (%)	Kappa Cohen (95% CI)	Adjusted Kappa PABAK (95% CI)
Anatomic site	91.1	0.783 (0.661 - 0.905)	0.823 (0.722 – 0.923)
Magnification	95.2	0.845 (0.725 - 0.965)	0.903 (0.828 – 0.979)
Image clarity	83.9	0.644 (0.503 - 0.785)	0.677 (0.548 – 0.807)
Angle	96.0	0.917 (0.846 - 0.988)	0.919 (0.850 – 0.989)
Sweep speed	98.4	0.849 (0.643 - 1.000)	0.968 (0.923 – 1.000)
Velocity and baseline	94.4	0.868 (0.774 - 0.962)	0.887 (0.806 – 0.968)

Table 6. Agreement between reviewers for each scoring criterion

Table 6 highlights that agreement amongst the individual scoring criteria, highest reliability was noted for the sweep speed adjustment (adjusted k = 0.968); and lowest reliability for the criterion of image clarity (adjusted k = 0.677).

Criteria interdependency was almost non-existent as demonstrated by the low or negative Cronbach a values for each individual criterion (Table 7).

	Cronbach's alpha for excluding each item individually	
	Reviewer A	**Reviewer B**
Anatomic site	0.123	-0.124
Magnification	0.341	0.323
Image clarity	0.118	0.031
Angle	0.269	0.162
Sweep speed	0.246	0.118
Velocity and baseline	0.107	-0.048
All six items	0.243	0.116

Table 7 Inter-item consistency amongst image scoring criteria for MCA Doppler image

5.2. PROJECT 2: DOPPLER REFERENCE RANGES AND CLINICAL IMPACT

This project is composed of two large studies carried out with the same methodology: on the one hand, we have studied the methodological quality of all studies published so far that establish reference values of fetal Doppler and, on the other, we have seen the great impact clinician who has the use of different reference values by performing a simulation in a group of real patients.

Two original articles, a letter to the editor, one oral communication in international congress and two in national congress and an editorial dedicated to one of our articles are part of this project.

Oros D, S, **Ruiz-Martinez S**, Staines-Urias E, Conde-Agudelo A, Villar J, Fabre E, Papageorghiou AT. Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio: a systematic review. Ultrasound Obstet Gynecol. 2019 Apr;53(4):454-464. doi: 10.1002/uog.20102

Estado: Publicado
Factor de impacto: 5.65
Primer cuartil

Ruiz-Martinez S, Papageorghiou AT, Staines-Urias E, Villar J, Gonzalez de Agüero R, Oros D. Clinical impact of Doppler reference charts to manage foetal growth restriction: the need for standardisation. Ultrasound Obstet Gynecol. 2019 Jun 25. doi: 10.1002/uog.20380.

Estado: Publicado
Factor de impacto: 5.65
Primer cuartil

Oral presentation: Revisión sistemática de la metodología usada para crear curvas de referencia de doppler fetal. 26º Congreso Nacional de la sección de medicina perinatal de la SEGO. Mayo 2018, Murcia.

Oral presentation: Clinical impact of the Doppler reference charts used for the management of fetal growth restriction: the need for standardisation. 27th World Congress on Ultrasound in Obstetrics and Gynecology. September 2017, Vienna (Austria)

Oral presentation: Valores normales para el índice de pulsatilidad de los vasos fetales y su repercusión clínica. 25º Congreso Nacional de la sección de medicina perinatal de la SEGO. Octubre 2016, Madrid.

Editorial: Systematic error and cognitive bias in obstetric ultrasound. A. Sotiriadis and A. O. Odibo. Ultrasound Obstet Gynecol 2019; 53: 431–435

Ultrasound in obstetrics and gynecology Journal Club April 2019: **FREE ACCESS**: Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio: a systematic review. Oros D, S, **Ruiz-Martinez S**, Staines-Urias E, Conde-Agudelo A, Villar J, Fabre E, Papageorghiou AT. Reference.

Factor de impacto: 5.65
Primer cuartil

a. MATERIAL AND METHODS

This study was conducted and reported in accordance with the checklist proposed by the MOOSE group(52) and the PRISMA statement for reporting systematic reviews and meta-analyses.(53)

Information sources and search strategy

A search strategy was formulated in collaboration with a professional information specialist (Table 8). Relevant studies were identified through a search of MEDLINE, EMBASE, CINAHL and the Web of Science databases including studies reported from 1954 through December 2016, extending until 2018 for the study of clinical impact. Reference lists of retrieved full-text articles were examined for additional relevant citations. The search was not restricted by study design or methodology.

MEDLINE AND EMBASE	Fetal Development/ exp Ultrasonography, Prenatal/ (ultrasound or ultrasonogra* or ultra-sound or ultra-sonogra* or sonogra* or echograph* or echogram?).mp. ultrasonography.fs. 3 or 4 (fetal or foetal or fetus* or foetus or prenatal* or pre-natal*).mp. 5 and 6 1 or 2 or 7 exp Ultrasonography, Doppler/ doppler.mp. 9 or 10 8 and 11 reference standards/ or reference values/ ((pulsatility or resistance or resistivity) adj2 (index or indices)).ti,ab. (normogra* or normality or (normal adj2 (range? or value? or standard? or reference? or index or indices or distribution))).ti,ab. (percentile? or centile?).ti,ab. (reference adj2 (curve* or chart* or index or indices or equation* or value* or range* or equation*)).ti,ab. (biometr* adj2 (curve* or chart* or index or indices or equation* or value* or range* or equation*)).ti,ab. ((middle artery or uterine artery) and (range? or value? or standard? or reference? or index or indices or distribution)).ti,ab. 13 or 14 or 15 or 16 or 17 or 18 or 19 12 and 20 exp animals/ not humans.sh. 21 not 22
CINAHL	S10 S6 AND S9 S9 S7 OR S8 S8 (((pulsatility or resistance or resistivity) N2 (index or indices))) OR ((normogra* or normality or (normal N2 (range? or value? or standard? or reference? or index or indices or distribution)))) OR (percentile? or centile?) OR ((reference N2 (curve* or chart* or index or indices or equation* or value* or range* or equation*))) OR ((biometr* N2 (curve* or chart* or index or indices or equation* or value* or range* or equation*))) OR (((middle artery or uterine artery) and (range? or value? or standard? or reference? or index or indices or distribution))) S7 (MH "Reference Values") S6 S4 AND S5 S5 (MH "Ultrasonography, Doppler+") OR TI doppler OR AB doppler S4 S1 OR S2 OR S3 S3 (ultrasound or ultrasonogra* or ultra-sound or ultra-sonogra* or sonogra* or echograph* or echogram*) AND (fetal or foetal or fetus* or foetus or prenatal* or pre-natal*) S2 (MH "Ultrasonography, Prenatal+") S1 (MH "Fetal Development")
WOK	# 1 TOPIC: (ultrasound or ultrasonogra* or ultra-sound or ultra-sonogra* or sonogra* or echograph* or echogram*) AND TOPIC: (fetal or foetal or fetus* or foetus or prenatal* or pre-natal*) AND TOPIC: (doppler) # 2 TOPIC: (((pulsatility or resistance or resistivity) NEAR/2 (index or indices))) OR TOPIC: (nomogram* OR nomograph*) OR TOPIC: ((normal NEAR/2 (range? or value? or standard? or reference? or index or indices or distribution))) OR TOPIC: (percentile* OR centile*) OR TOPIC: ((reference NEAR/2 (curve* or chart* or index or indices or equation* or value* or range* or equation*))) OR TOPIC: ((biometr* NEAR/2 (curve* or chart* or index or indices or equation* or value* or range* or equation*))) OR TOPIC: ((("middle artery" or "uterine artery") NEAR/2 (range? or value? or standard? or reference? or index or indices or distribution))) # 3 #2 AND #1

Table 8. Search strategy

Eligibility criteria and study selection

Inclusion criteria

- Observational (cohort or cross-sectional) studies aimed to create references ranges for Doppler indices of UA, MCA, and CPR.
- Only articles published in English or Spanish were considered

Exclusion criteria

- Case-control studies
- The primary aim was not to construct Doppler reference ranges
- Studies limited to less than 20 weeks or more than 40 weeks

The first search yielded 2902 citations, of which 56 were considered for potential inclusion and finally, only 38 studies were included. The flow chart of the literature search is presented in Figure 13. All of the potentially relevant studies were retrieved and reviewed independently by two authors (SR-M and DO) to determine the inclusion. Disagreements were resolved through consensus.

From the same bibliographic search, we obtain different results since for the study "Clinical impact of Doppler reference charts to manage foetal growth restriction" the search was updated extending the last two years, getting 2968 after removed duplicated and no journal articles, 58 studies were selected to full text analysis and, finally, 40 studies were included. For the analysis of the clinical impact, the same studies were included as for the quality analysis, adding two recent studies. Figures 13 and 14 represent the studies obtained and the selection of the studies chosen to analyze. In

addition to the clinical impact study, the 10 most cited were selected as representatives of the most commonly used reference values.

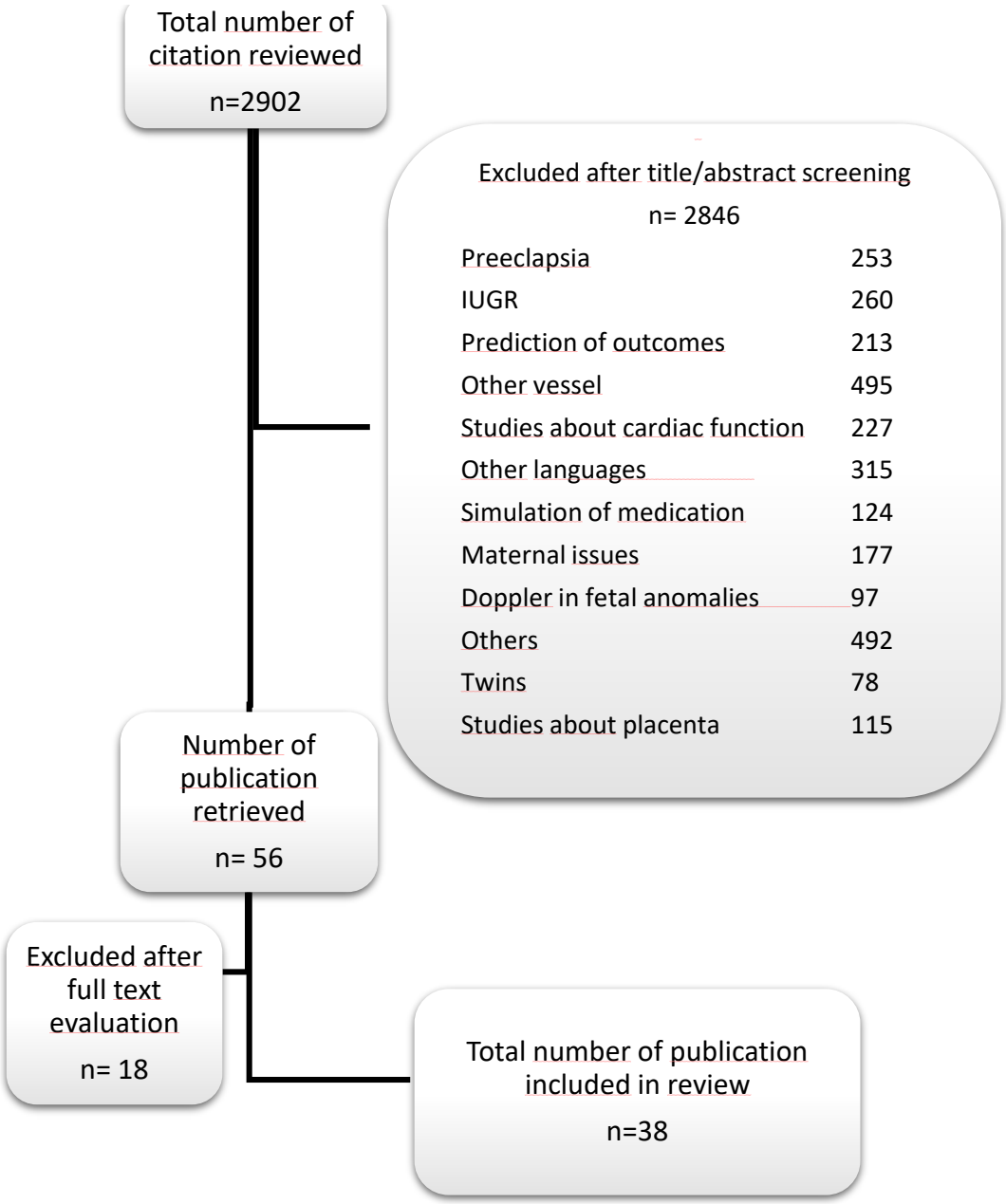


Figure 13. Flow chart 1: Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio.

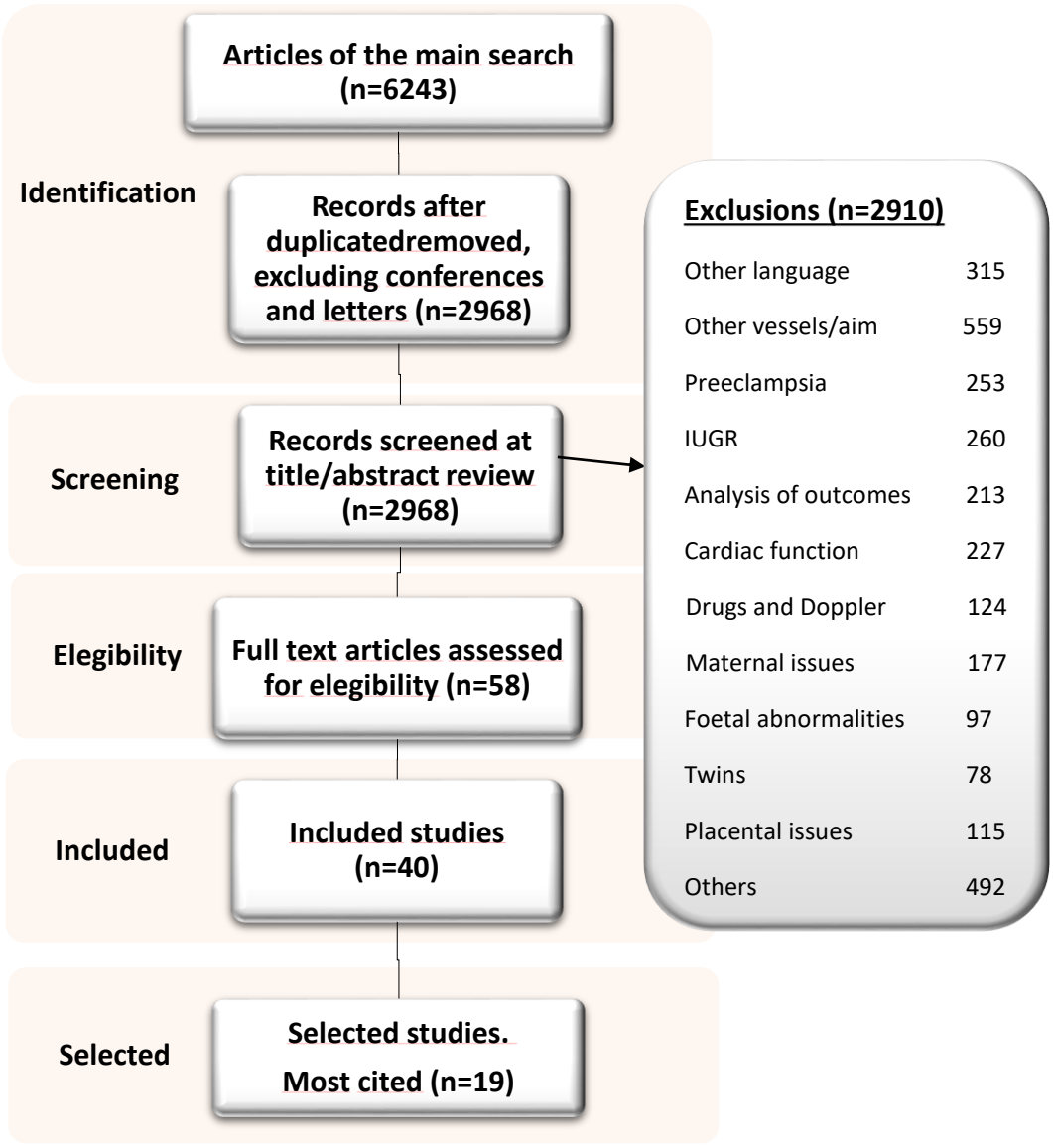


Figure 14. Flow chart 2: Clinical impact of Doppler reference charts to manage foetal growth restriction

Excluded from this review and the reasons for exclusion are listed in table 9.

AUTHOR AND YEAR	REASONS FOR EXCLUSION
DeVore 2015(46)	Review about CPR in SGA foetuses
Tavares et al 2012(66)	Written in Portuguese
McCarthy et al 2013(67)	Difference among members and fellows of RANZCOG
Rujiwetpongstorn et al 2007(68)	11 and 20 weeks of gestation
Simanaviciute et al 2006(69)	Comparison between normal pregnancies and preeclampsia pregnancies
Acharya et al 2005(70)	Comparison of measurements in three different sites of umbilical artery
Palacio et al 2004(71)	Prolonged pregnancies
Yagel et al 1999(72)	Values in a novel ultra- sound technology.
Morales-Rosello et al 1999(73)	Other vessel: foetal femoral artery
Lees et al 1999(74)	Umbilical artery and vein blood volume flow
Brackley et al 1998(75)	Use of the Laplace transform analysis technique
Luzi et al 1996(76)	Differences in the FVWs of the middle cerebral artery recorded on M1 and M2 segments
Joern et al 1996(77)	Doppler parameters (PI, RI or S/D ratio) not assessed.
Weissman et al 1994(78)	Assessment of vessel diameters.
Marsal 1994(79)	Review of different studies
Chandran et al 1993(80)	Comparison of computerised antenatal foetal heart rate (FHR) analysis with the MCA PI as indicators of foetal compromise
Mari et al 1991(81)	Comparison of AGA with SGA
Gudmundsson 1991(82)	Prediction of adverse outcomes in IUGR

Table 9. Excluded studies

Methodological quality assessment: Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio

A list of methodological quality criteria (Table 10) was initially developed by one of the authors of the present study (AC-A), modified for use in the setting of Doppler and agreed by the team not involved in data abstraction. These quality criteria are based on available published research(54,57,83), and are divided into two domains: study design and statistical and reporting methods; in total, 24 quality criteria were evaluated.

The methodological quality of the full-text versions of eligible studies was independently assessed by the same reviewers and a medical statistician (ES-U). Disagreements were resolved by consensus or consultation with two other reviewers (ATP and EF).

Authors' institutions were contacted in order to obtain a copy of the published article where this was not available from library sources.

DOMAIN	LOW RISK OF BIAS	HIGH RISK OF BIAS
1.- STUDY DESIGN		
1.1 Design	Clearly described as either cross-sectional or longitudinal	Not reported Mixture of cross-sectional and longitudinal data
1.2 Population	Women were reported as coming from a population at low risk of pregnancy complications	Women come from an unselected population; or were selected: or at hish risk of pregnancy complications; or not reported.
1.3 Prospective data collection	Prospective study and ultrasound data collected specifically for the purpose of constructing charts of fetal Doppler	Retrospective study, or data not collected specifically for the purpose of constructing charts of fetal Doppler, or unclear (e.g. use of routinely collected data)
1.4 Specific scan	Specific scan for research purposes	Routine scan in context of pregnancy assessment
1.5 Sample size	A priori determination or calculation of sample size and justification.	Lack of a priori sample size determination or calculation and justification
1.6 Recruitment period	Reported in months	Not reported
1.7 Consecutive enrolment	Consecutively included patients	Not consecutively included patients
1.8 Inclusion/ exclusion criteria	The study made it clear that women at high risk of pregnancy complications were not included, and that women with abnormal outcome were excluded, i.e. an effort was made to include 'normal' outcome as best possible. As a minimum, the study population should exclude: – multiple pregnancy – fetuses with congenital structural or chromosomal anomalies – fetal death/stillbirth – women with disorders that may affect fetal growth or Doppler (at least should specify exclusion of women with pre-existing hypertension, diabetes mellitus, renal disease and smoking) – pregnancy complications (at least pre-eclampsia, SGA/IUGR, prematurity, diabetes mellitus,) – deliveries prior 37 weeks	The study population included both low-risk and high-risk pregnancies, or women with abnormal outcome were not excluded. Study population that did not exclude foetuses or women with the characteristics previously described. Exclusions which would have a direct effect on the Doppler, such as foetuses found at birth to be small for dates.

1.9 Method of dating pregnancy	Clearly described Known last menstrual period (LMP) and a sonogram before 14 weeks demonstrating a crown–rump length (CRL) that corroborates LMP dates (within how many days unspecified)	Not described clearly Gestational age assessment at >14 weeks, or gestational age assessment not including ultrasonographic verification
1.10 Multicentre study	Study performed with more than one centre collaborating.	Only one hospital.
2.- REPORTING AND STATISTICAL METHODS	**Low risk of bias**	**High risk of bias**
2.1 Perinatal outcomes	Prospectively collected and reported	Not reported
2.2 Gestational age range	Reported	Not reported
2.3 Ultrasound machine(s) used and probe type	Clearly specified	Not clearly specified
2.4 Reported sonographers	Number of sonographers reported	Not clearly specified
2.5 Sonographers experience	Experienced or specifically trained sonographers clearly reported	Not clearly specified
2.6 Blinded measurements	Sonographers were blinded	Not clearly specified
2.7 Contains quality control measures	Should include the following: – assessment of intraobserver variability – assessment of interobserver variability – image review – image scoring – image storage	Does not contain quality control measures
2.8 Protocol	The study described sufficient and unambiguous details of the measurement techniques used for fetal Doppler parameters.	The study did not describe sufficient and unambiguous details of the measurement techniques used for fetal Doppler parameters
2.9 Number of measurements taken for each Doppler variable	At least three measures per fetus per scan	Single measure or not specified

2.10 Angle correction	Clearly specified	Not clearly specified
2.11 Statistical methods	Clearly described and identified	Not clearly described and identified
2.12 Report of mean and SD of each measurement and the sample size for each week of gestation	Presented in a table or clearly described	Not presented in a table or not clearly described
2.13 Report of regression equations for the mean (and SD if relevant) for each measurement)	Reported	Not reported
2.14 Scatter diagram	Study included Doppler Chart with mean and SD or centiles, at less 5th centile, 50th and 95th centile.	Doppler Charts not included

Table 10. Methodological quality criteria

Clinical simulation: "Clinical impact of Doppler reference charts to manage foetal growth restriction"

The 10 most cited studies were selected for each vessel to compare the most used published Doppler reference standards. An UA PI over the 95th percentile and MCA PI and CPR below the 5th percentile was considered to be clinically relevant cut-off values.(17,32,84) Clinical cut-off percentiles were calculated by the mean and standard deviation for gestational age when not reported by the authors.(85) Variability was expressed as a percentage and was obtained by subtracting the lowest PI value from the highest and dividing by the highest PI value for every week of gestation.

Simulation analysis was performed on a cohort of 617 consecutive foetuses with an estimated foetal weight (EFW) below the 10th percentile(59), assessed in our centre from 24–41 weeks of gestation. IUGR was defined as an EFW below the 10th percentile accompanied with whichever abnormal Doppler PI(s) (UA>95th, MCA<5th, or CPR<5th); in which labour induction was recommended at 37 weeks of gestation.(17,32,84)

To assess the influence of the Doppler reference standard variability in the clinical management of SGA foetuses, every case was hypothetically classified and theoretically managed according to the same previously described protocol, using the highest and lowest PI cut-off values for the UA, MCA, and CPR for every gestational age.

b. STATISTICAL ANALYSIS

All study details were entered into a Microsoft Excel 2010 spread sheet. Every study was assessed against each of the criteria within the checklist and were scored as either 0 or 1 if there was a 'high' or 'low' risk of bias, respectively. The overall quality score was defined as the sum of 'low risk of bias' marks (with the range of possible scores being 0–24). In order to assess agreement between reviewers in defining high or low risk of bias we calculated the Intraclass correlation coefficient (ICC) of the inter observer complete score; this suggested excellent agreement (0.815, 95% CI 0.66-0.90).

Multiple regression analysis was performed between quality scores and study characteristics which were not part of the scoring algorithm: year of publication, sample size of participating women, sample size of included ultrasound examinations, study duration, type of participating hospitals (teaching versus non-teaching), number of participating sites (single versus multi-site), and number of sonographers (single versus multiple).

Statistical analyses were performed using Microsoft Excel 2010 and IBM SPSS Statistics version 20 (IBM, Armonk, NY).

c. RESULTS

"Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio: a systematic review"

A total of 38 studies from 22 countries met the inclusion criteria and were included in the final analysis. The main characteristics and overall, study design and statistical and reporting methods quality scores for each study included are presented in the following table. (Table 11)

- The overall mean quality score for the included studies was 51.4% (95% Confidence interval (CI) 47.1 - 55.8)
    - Mean of quality scores for study design was 47.4% (42.6 - 52.1).
    - Mean of quality scores for statistical and reporting methods was 54.3% (48.8 - 59.7)
- The earliest study was published in 1988(86) and the latest in 2016.(87)
- The median sample size of participating women was 206 (range, 13-2323, interquartile range, 605),
- The median number of ultrasound examinations was 513 (range, 60-2323; interquartile range, 742).
- UA Doppler reference ranges were reported in 30 studies.
- MCA Doppler reference ranges were reported in 19 studies.
- In 11 studies reference ranges for both UA and MCA were reported.
- Only 4 studies reported reference ranges for CPR.
- The indices reported were the PI in 31 studies, the resistance index (RI) in 21 and the systolic-diastolic ratio (S/D) in 21 studies.

The overall methodology score was similar for the studies focused on UA (median 49.0%; range 20.8-70.8), MCA (median 55.0%; range 29.1-79.1) and CPR (median 54.1%; range 41.6-62.5).

Study	Year	Country	Study period-months	Women (n)	Number of scan	Weeks	Study design	Vess-els	Doppler parame-ters	Data colle-ction	Methods score	Design score	Total score
Seffah et al(87)	2016	Ghana	5	470	458	20-40	CS	MCA	PI, RI, S/D	P	78,57 (11/14)	70 (7/10)	75 (18/24)
Ayoola et al(88)	2016	Nigeria	12	400	400	15-39	CS	UA	PI, RI, S/D	P	64,28 (9/14)	50 (5/10)	58,33 (14/24)
Morales-rosello et al(89)	2014	Spain	NR	2323	2323	19-41	CS	MCA CPR	PI	NR	50 (7/14)	30 (3/10)	41,66 (10/24)
Ferdousi et al(90)	2013	Banglades h	12	60	60	NR	CS	UA	PI, RI	NR	14,28 (2/14)	30 (3/10)	20,83 (5/24)
Bahlmann et al(91)	2012	Germany	NR	1926	1926	18-42	CS	UA	PI, RI	P	57,14 (8/14)	40 (4/10)	50 (12/24)
Sutantawib oon et al(92)	2011	Thailand	12	658	658	13-40	CS	UA	PI, RI S/D	P	35,71 (5/14)	40 (4/10)	37,50 (9/24)
Tarzamni et al(93)	2009	Iran	40	978	978	20-40	CS	MCA	PI, RI, S/D RATIO	P	64,28 (9/14)	60 (6/10)	62,50 (15/24)
Tarzamni et al(94)	2008	Iran	40	978	978	20-40	CS	MCA	PI, RI, S/D	P	71,42 (10/14)	60 (6/10)	66,66 (16/24)
Parra-cordero et al(95)	2007	UK	18	172	172	23-41	CS	UA MCA	PI	P	64,28 (9/14)	60 (6/10)	62,50 (15/24)
Ebbing et al(96)	2007	Norway	NR	161	566	19-41	Ll	UA MCA CPR	PI	P	64,28 (9/14)	60 (6/10)	62,50 (15/24)
Medina castro et al(97)	2006	España/ Mexico	30	2081	2081	20-40	CS	UA	PI	P	64,28 (9/14)	80 (8/10)	70,83 (7/24)

Study	Year	Country	Study period-months	Women (n)	Number of scan	Weeks	Study design	Vess-els	Doppler parame-ters	Data collect-ion	Methods score	Design score	Total score
Medina castro et al(98)	2006	España/ Mexico	31	727	727	20-40	CS	MCA	PI	P	78,57 (11/14)	80 (8/10)	79,16 (19/24)
Konje et al(99)	2005	UK	NR	70	NR	24-38	L	UA, MCA	PI, RI, S/D	P	71,42 (10/14)	50 (5/10)	62,50 (15/24)
Acharya et al(100)	2005	Norway	NR	130	513	19-42	L	UA	PI, RI, S/D	P	64,28 (9/14)	40 (4/10)	54,16 (13/24)
Komwilaisak et al(101)	2004	Thailand	6	312	312	20-37	CS	MCA	PI	P	50 (7/14)	80 (8/10)	62,50 (15/24)
Ertan et al(102)	2003	NR	NR	370	602	28-40	CS	UA, MCA	PI, RI, S/D	P	21,42 (3/14)	40 (4/10)	29,16 (7/24)
Baschat et al(103)	2003	Germany	NR	306	306	20-40	CS	UA, MCA, CPR	PI	P	57,14 (8/14)	40 (4/10)	50 (12/24)
Bahlmann et al(104)	2002	Germany	NR	926	926	18-42	CS	MCA	PI, RI	P	78,57 (11/14)	50 (5/10)	66,66 (16/24)
Meyberg et al(105)	2000	Germany	NR	70	600	28-40	L	MCA	RI, S/D	P	21,42 (3/14)	40 (4/10)	29,16 (7/24)
Romero gutierrez et al(106)	1999	Mexico	NR	60	337	30-40	L	UA	PI, RI	P	42,85 (6/14)	60 (6/10)	50 (12/24)
Lahkar et al(107)	1999	India	12	71	NR	20-34	L	UA	PI, RI, S/D	P	28,57 (4/14)	40 (4/10)	33,33 (8/24)
Owen et al(108)	1997	UK	NR	274	NR	26-41	L	UA	PI, S/D	P	42,85 (6/14)	50 (5/10)	45,83 (11/24)
Kurmanavicius et al(109)	1997	Switzerland	NR	1675	1675	24-42	CS	UA, MCA, CPR	RI	P	71,42 (10/14)	40 (4/10)	58,33 (14/24)

Study	Year	Country	Study period-months	Women (n)	Number of scan	Weeks	Study design	Vess-els	Doppler parame-ters	Data collect-ion	Methods score	Design score	Total score
Manabe et al(110)	1995	Japan	NR	13	195	15-40	L	UA, MCA	PI	P	57,14 (8/14)	40 (4/10)	50 (12/24)
Rizzo et al(62)	1994	Italy	NR	153	153	18-42	CS	UA, MCA	PI	R	35,71 (5/14)	40 (4/10)	37,50 (9/24)
Dilmen et al(111)	1994	Turkey	11	550	550	16-41	CS	UA	PI, RI, S/D	P	42,85 (6/14)	40 (4/10)	41,66 (10/24)
Rodriguez ballesteros et al(112)	1993	Mexico	12	123	335	20-40	UC	UA	S/D	P	78,57 (11/14)	50 (5/10)	66,66 (16/24)
Duggan et al(113)	1993	New Zeland	NR	19	NR	18-40	L	UA	RI	P	42,85 (6/14)	40 (4/10)	41,66 (10/24)
Bruner et al(114)	1993	USA	10	122	122	16-43	CS	UA	S/D	UC	64,28 (9/14)	30 (3/10)	50 (12/24)
Kofinas et al(115)	1992	USA	NR	154	154	16-42	CS	UA	RI, S/D	P	64,28 (9/14)	30 (3/10)	50 (12/24)
Pattinson et al(116)	1989	South Africa	NR	45	NR	20-38	L	UA	PI, RI, S/D	P	50 (7/14)	50 (5/10)	50 (12/24)
Pearce et al(117)	1988	UK	NR	34	NR	16-40	L	UA	PI, RI, S/D	P	57,14 (8/14)	40 (4/10)	50 (12/24)
Gerson et al(118)	1987	USA	NR	171	NR	20-40	CS	UA	S/D	P	50(7/14)	50(5/10)	50(12/24)
Arduini et al(62)	1990	Italy	NR	1556	1556	20-42	CS	UA, MCA	PI	P	57,14 (8/14)	60 (6/10)	58,33 (14/24)
Arstrom et al(119)	1989	Sweden	NR	22	NR	24-42	L	UA, MCA	PI, RI, S/D	P	57,14 (8/14)	40 (4/10)	50 (12/24)
Fogarty et al(120)	1990	Ireland	NR	85	783	16-42	L	UA	PI, RI, S/D	P	57,14 (8/14)	50 (5/10)	54,16 (13/24)

Study	Year	Country	Study period-months	Women (n)	Number of scan	Weeks	Study design	Vess-els	Doppler parame-ters	Data collect-ion	Methods score	Design score	Total score
Ferrazzi et al(121)	1990	Italy	NR	482/150	NR	18-38	CS/ LI	UA, MCA	PI, S/D	P	57,14 (8/14)	30 (3/10)	45,83 (11/24)
Wladimiroff et al(86)	1988	Nether-lands	NR	240	225	26-39	CS	UA	PI	P	35,71 (5/14)	20 (2/10)	29,16 (7/24)

Table 11 Included Studies – Quality scores for Study Design and reporting and statistical methods. P=Prospective; CS=Cross sectional; L=Longitudinal; UC=Unclear

Data collection was prospective in 34 studies, but only in 19 studies was data collection explicitly for research purposes (Figure 15A; Table 11). Thirteen studies had a longitudinal design, 23 were cross-sectional, and one was mixed (cross-sectional and longitudinal); the design of the remaining study was not reported. Low-risk pregnancies were included in 22 (57.9%) studies. About half of the studies (52%) used a dating method considered to be at low risk of bias, namely either first trimester measurement of crown rump length (CRL) alone or the maternal last menstrual period confirmed by CRL. Overall, the demographic characteristics of the populations and any inclusion or exclusion criteria were not described in detail.

The frequencies of "low risk of bias" in each of the three groups of methodological criteria for the UA, MCA and CPR are presented in Figures 15-17. The highest risk of bias was similar for the UA, MCA and CPR, and was noted in the following fields: "Multicentre study", where only three of the studies were performed in more than one centre (Figures 15-17, item 1.10); "Ultrasound quality control measures", where only two studies focused on the UA demonstrated a comprehensive quality assurance strategy, and where no study reported the use of an image scoring method for the purpose of ultrasound quality assurance (Figures 15-17, item 2.7); "Sonographer experience", where only three and four studies of UA and MCA Doppler, respectively, clearly specified the experience or training of the sonographers (Figures 15-17, item 2.5); "Blinded measurements", where in only one UA study sonographers were blinded to the measurement recorded during the examination. (Figures 15-17, item 2.6); and "Number of measurements", which was apparent in only three studies (Figures 15-17, item 2.9). Furthermore, none of the CPR studies reported information on "Recruitment period" (Figure 17, item 1.6).

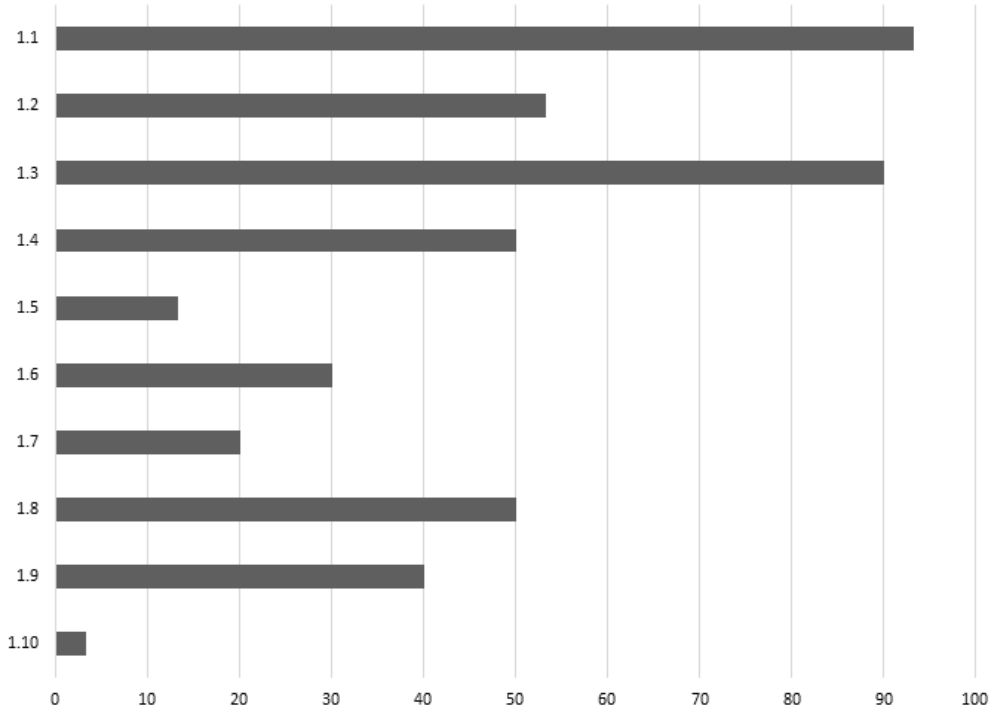
Although some individual criteria of participant selection were used in different studies, there was no study in which all of these criteria were systematically used. (Figures 15-17, item 1.8). In the same line, sample size calculation was apparent in only seven studies (18,4%) (Figures 15-17, item 1.5).

Results from individual studies were reported in the form of tables, equations or charts as shown in Figures 15-17. Tables of mean and standard deviation (SD) of each measurement and for each week of gestation were the most common methods of presentation (24 studies).

An equation for the mean and SD was reported in 23 of 38 studies, whereas printed charts of the median and percentile curves were seen in 25 publications.

With regard to type of hospital, teaching (N=28) did not have significantly higher overall quality scores as compared to non-teaching (N=10) hospitals (52.2% vs. 48.3%; p=0.4). In line with these results, but contrary to similar previous reports(22), neither the year of publication (p=0.506) nor the sample size of participating women (p=0.119), ultrasound examinations (p=0.215), study duration (p=0.251), teaching hospital (p=0.395), number of participating sites (p=0.278) or sonographers (p=0.447) were significant predictors of quality score both on univariate or multiple regression analysis.

A. Study design



B. Reporting and statistical

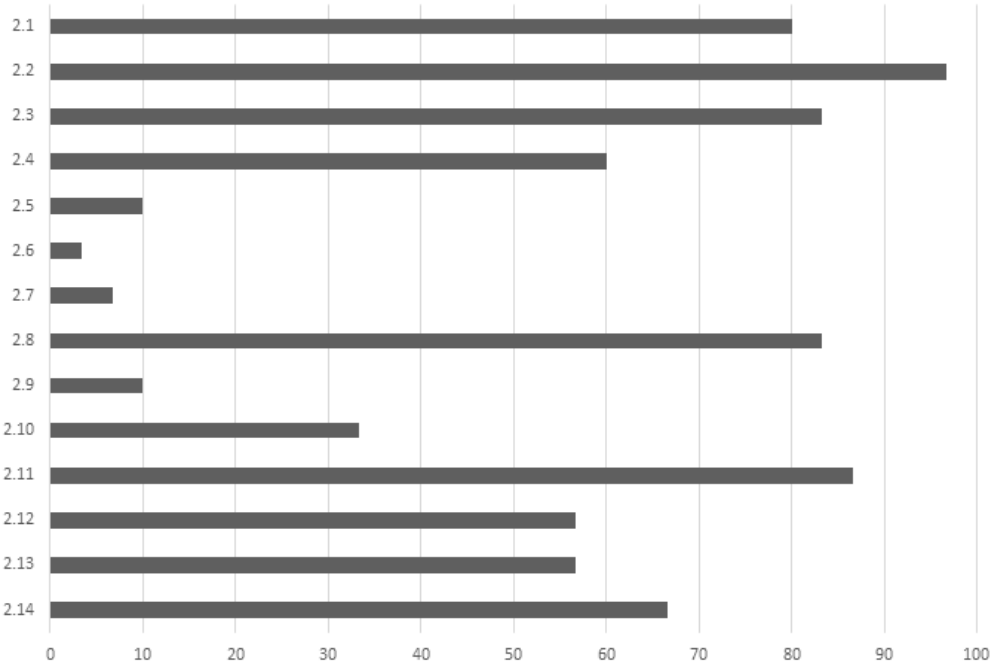
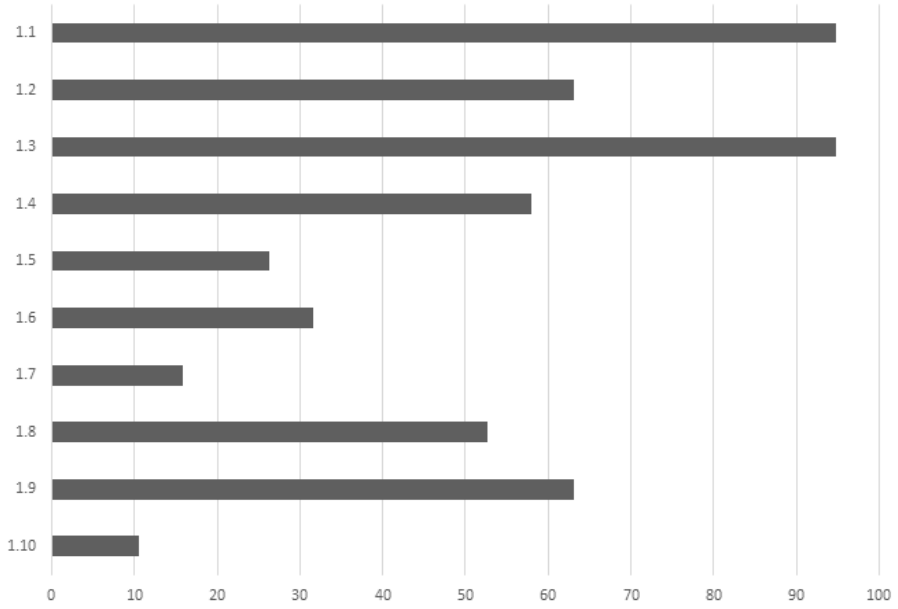


Figure 15. Overall methodological quality of umbilical artery studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

A. Study design



B. Reporting and statistical methods

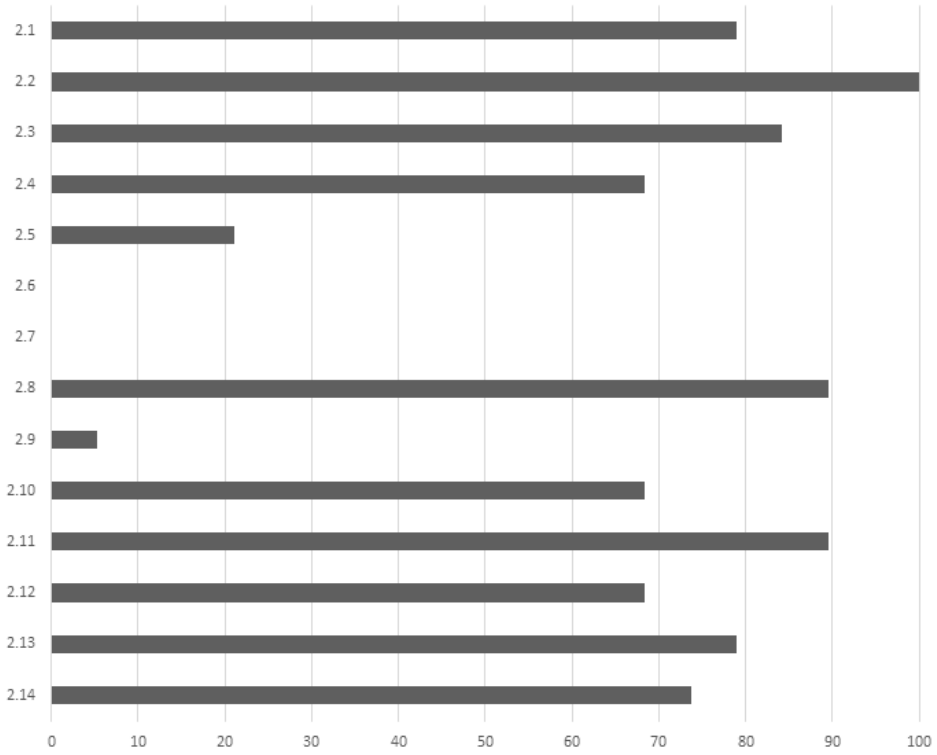
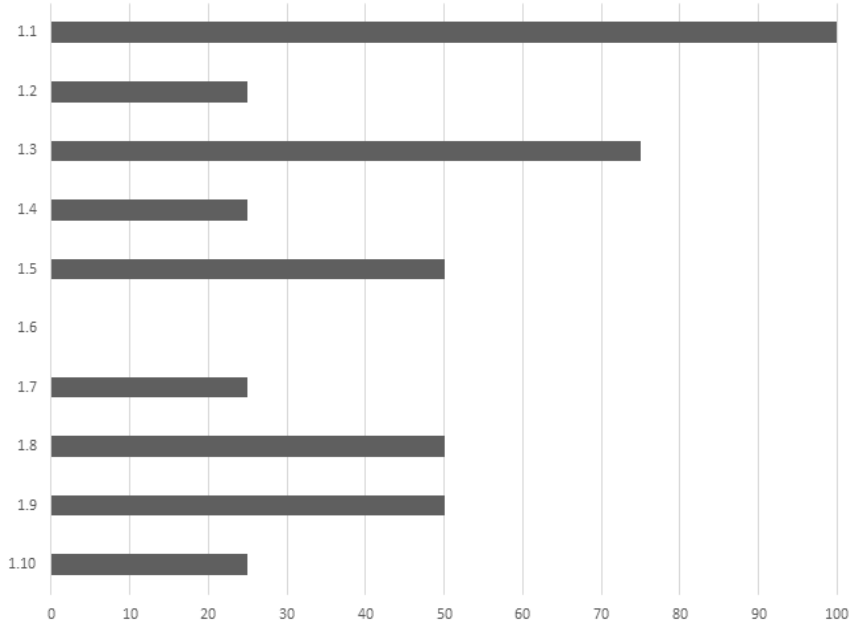


Figure 16. Overall methodological quality of middle cerebral artery studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

A. Study design



B. Reporting and statistical methods

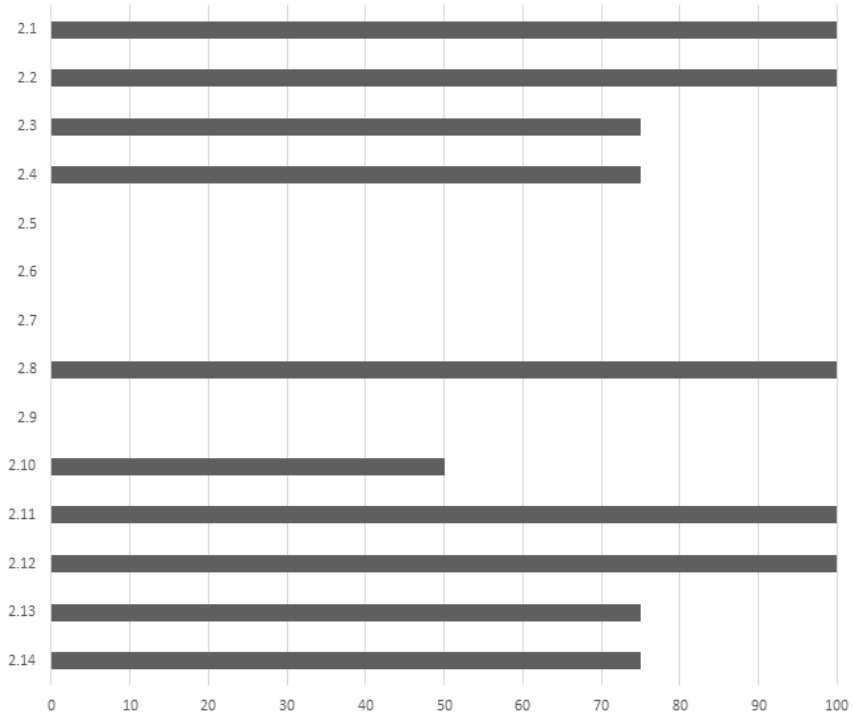


Figure 17. Overall methodological quality of cerebroplacental ratio studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

The following table (table 12) shows the reference values established by the studies with the highest methodological quality score according to the weeks of gestation, from week 28 to 41. Differences in the studies that had the highest scores for quality UA, MCA and CPR showed that significant heterogeneity remained: for example, the 95th centile of UA PI at 37 weeks of gestation was 1.41 in one chart(62), whereas the same cut-off value was 1.1 in another(95).[46] Standard situations were also noted at various other gestational ages and in reference ranges for MCA and CPR.

Gestational age,	Umbilical Artery PI						Middle Cerebral Artery PI						Cerebroplacental ratio					
	Medina Castro et al(97)		Parra-cordero et al(95)		Arduini et al(62)		Medina Castro et al(98)		Seffah et al(87)		Bahlman et al(104)		Morales-Rosello (89)		Ebbing(96)		Baschat (103)	
	50th	95th	50th	95th	50th	95th	50th	5th	50th	5th	Mean	5th	50th	5th	50th	5th	Mean	5th
28	1,06	1,41	1,07	1,45	1,12	1,61	1,77	1,17	1,96	1,03	1,94	1,44	1,73	1,23	2,14	1,47	2,13	1,28
29	1	1,46	1,04	1,4	1,08	1,57	1,89	1,12	1,92	0,91	1,94	1,44	1,76	1,25	2,21	1,53	1,86	1,15
30	1,03	1,39	1,01	1,36	1,05	1,54	1,92	1,18	1,75	1,42	1,92	1,42	1,79	1,25	2,28	1,58	2,34	1,44
31	1,03	1,37	0,98	1,32	1,02	1,51	1,93	1,14	1,77	1,51	1,9	1,40	1,81	1,26	2,32	1,62	2,29	1,73
32	1	1,35	0,95	1,28	0,99	1,48	1,82	1,15	1,54	1,41	1,88	1,37	1,82	1,26	2,35	1,64	2,03	1,24
33	0,96	1,3	0,92	1,24	0,97	1,46	1,8	1,11	1,66	1,11	1,74	1,33	1,82	1,25	2,36	1,65	2,1	1,44
34	0,97	1,29	0,89	1,2	0,95	1,44	1,7	1,12	1,52	1,29	1,8	1,28	1,81	1,24	2,35	1,63	2,1	1,36
35	0,93	1,27	0,86	1,17	0,94	1,43	1,63	1,07	1,32	1,08	1,75	1,23	1,79	1,22	2,32	1,6	2,01	1,45
36	0,92	1,21	0,84	1,13	0,92	1,42	1,6	0,99	1,38	1,03	1,68	1,16	1,77	1,2	2,27	1,55	2,01	1,26
37	0,86	1,18	81	1,1	0,92	1,41	1,45	0,85	1,53	1,01	1,61	1,09	1,73	1,17	2,19	1,48	2,25	1,17
38	84	1,12	79	1,06	0,91	1,4	1,37	0,79	1,14	0,96	1,53	1,01	1,69	1,14	2,09	1,4	1,9	1,23
39	0,83	1,05	0,76	1,03	0,91	1,4	1,24	0,75	1,37	0,77	1,45	0,92	1,64	1,1	1,97	1,29	1,64	1,16
40	0,79	1,07	0,74	1	0,91	1,4	1,06	0,56	0,99	0,92	1,35	0,82	1,58	1,06	-	-	1,8	1,08

Table 12. Values of the 50th centile and for clinically relevant cut-offs (in brackets) for UA (95th centile), MCA (5th centile) and CPR (5th centile) from the highest scoring studies

- ***"Clinical impact of Doppler reference charts to manage foetal growth restriction: the need for standardisation"***

Finally, forty studies met the selection criteria with their sole objective being to determine reference Doppler values, and were included

We selected the Doppler reference values most used in clinical practice and research.

Thus, we included the top 10 most cited Doppler reference values for MCA and CPR PIs. However, because four articles focused on UA presented the same number of citations, we included 13 UA Doppler reference values instead of 10 to avoid selection bias. We only found five articles showing reference ranges of CPR. Table 13 describes the main characteristics and number of citations of the 19 selected studies.

REFERENCE	YEAR	PATIENTS (N)	SCANS (N)	WEEKS	STUDY	NO. OF CITATIONS (N)	DOPPLER
Arduini et al(62)	1990	1556	1556	20-42	CS	325	UA/MCA
Baschat et al(103)	2003	306	306	20-40	CS	199	UA/MCA/CPR
Acharya et al (100)	2004	130	513	19-41	L	161	UA
Ebbing et al(96)	2007	161	566	21-39	L	86	MCA/CPR
Wladimiroff et al(86)	1988	284	284	26-38	CS	43	UA
Bahlman et al(104)	2002	926	926	18-42	CS	59	MCA
Parra-cordero et al(95)	2007	172	172	23-40	CS	37	UA/MCA
Manabe et al(110)	1995	20	195	15-40	L	16	UA
Fogarty et al(120)	1990	85	783	16-42	L	13	UA
Tarzamni et al(93)	2009	1037	1037	20-40	CS	9	MCA
Morales-rosello et al(89)	2015	2323	2323	19-41	CS	5	MCA/CPR
Medina castro et al(97)	2006	2081	2081	20-40	CS	5	UA
Medina castro et al(98)	2006	727	727	20-40	CS	4	MCA
Komwilaisak et al(101)	2004	312	312	20-37	CS	4	MCA
Bahlman et al(91)	2012	1926	1926	18-40	CS	3	UA/MCA
Romero et al(106)	1999	60	337	30-40	L	0	UA
Ayoola et al(88)	2016	400	400	15-39	CS	0	UA
Srikumar et al(122)	2017	200	773	19-40	L	0	UA/CPR
Ciobanu et al(123)	2018	72417	72417	20-41	CS	0	UA/CPR

Table 13. Main characteristics of the included studies. CS=Cross sectional; L= Longitudinal

The distribution of UA PIs within the 95th percentile across all pregnancies for each study is plotted in Figure 18. Similarly, PIs for MCA and CPR within the 5th percentiles were plotted and are shown in Figures 19 and 20. Notably, great variability existed between the reference values for the different Doppler PI cut-offs, with clinical implications. Furthermore, many of the most cited references in the literature showed an anomalous distribution of their PI cut-off values during gestation, possibly due to inappropriate statistical analyses.

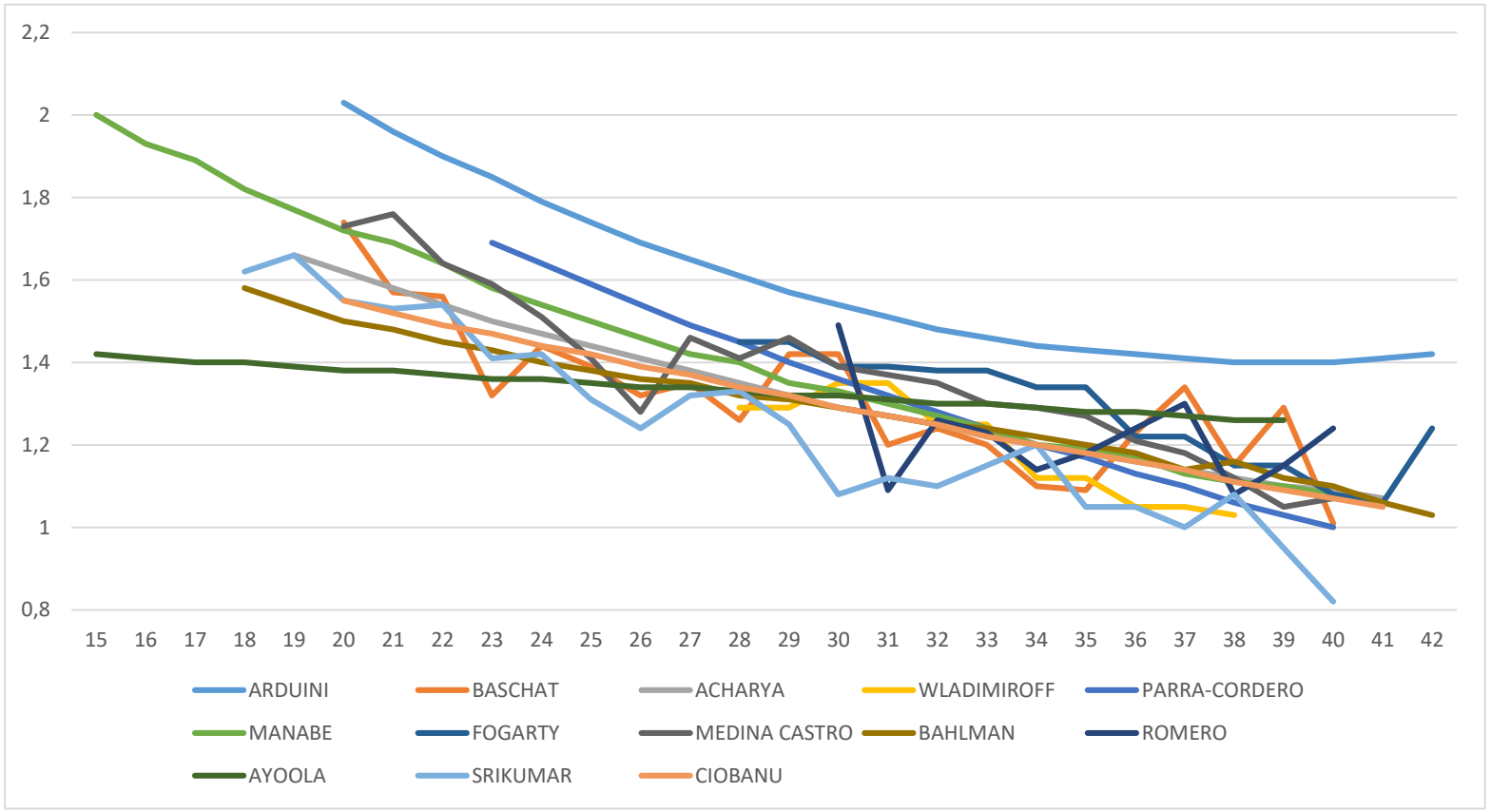


Figure 18. Pulsatility index above the 95th percentile of the most cited umbilical artery reference standards throughout the pregnancy.

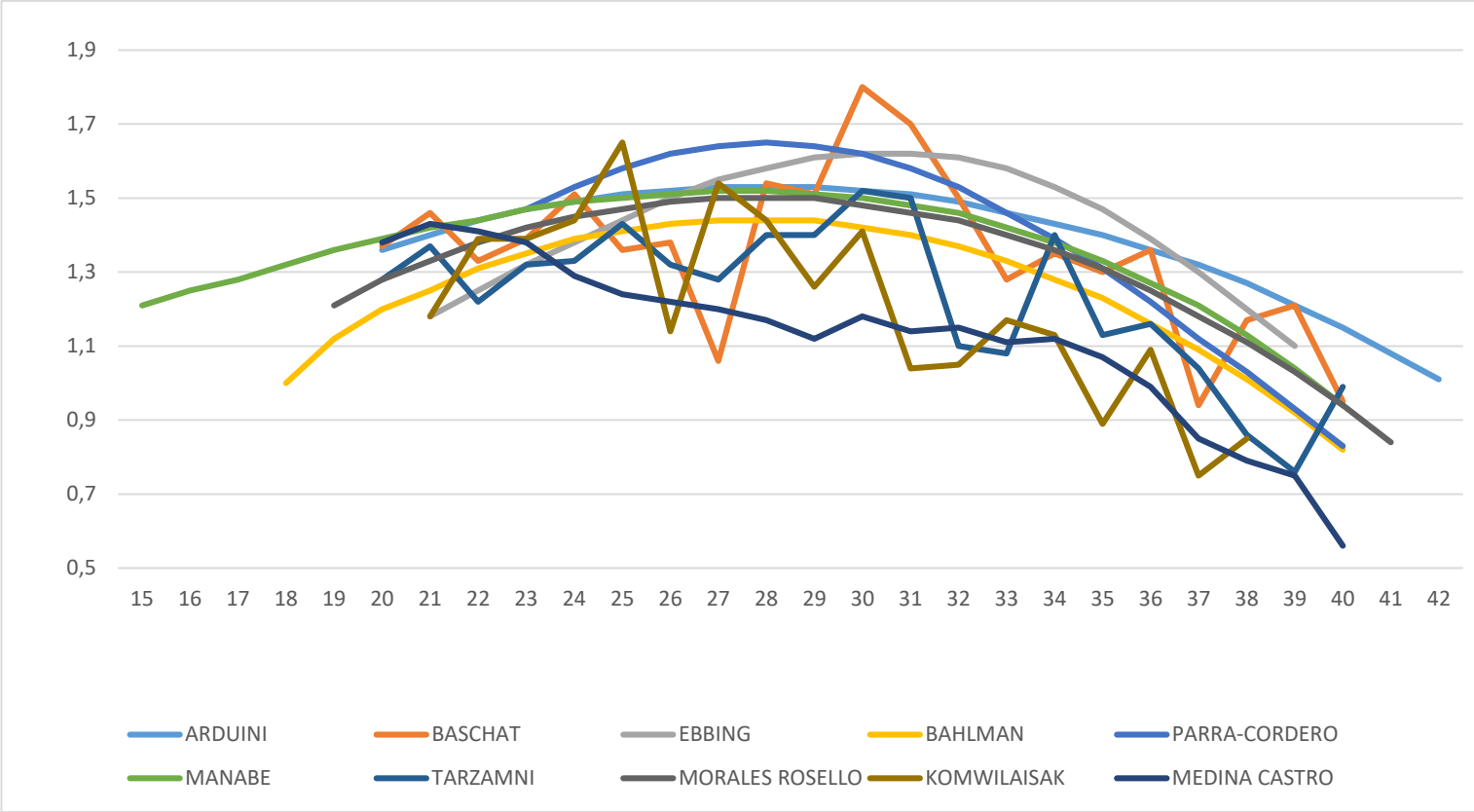


Figure 19. Pulsatility index below the 5th percentile of the most cited middle cerebral artery reference standards throughout the pregnancy.

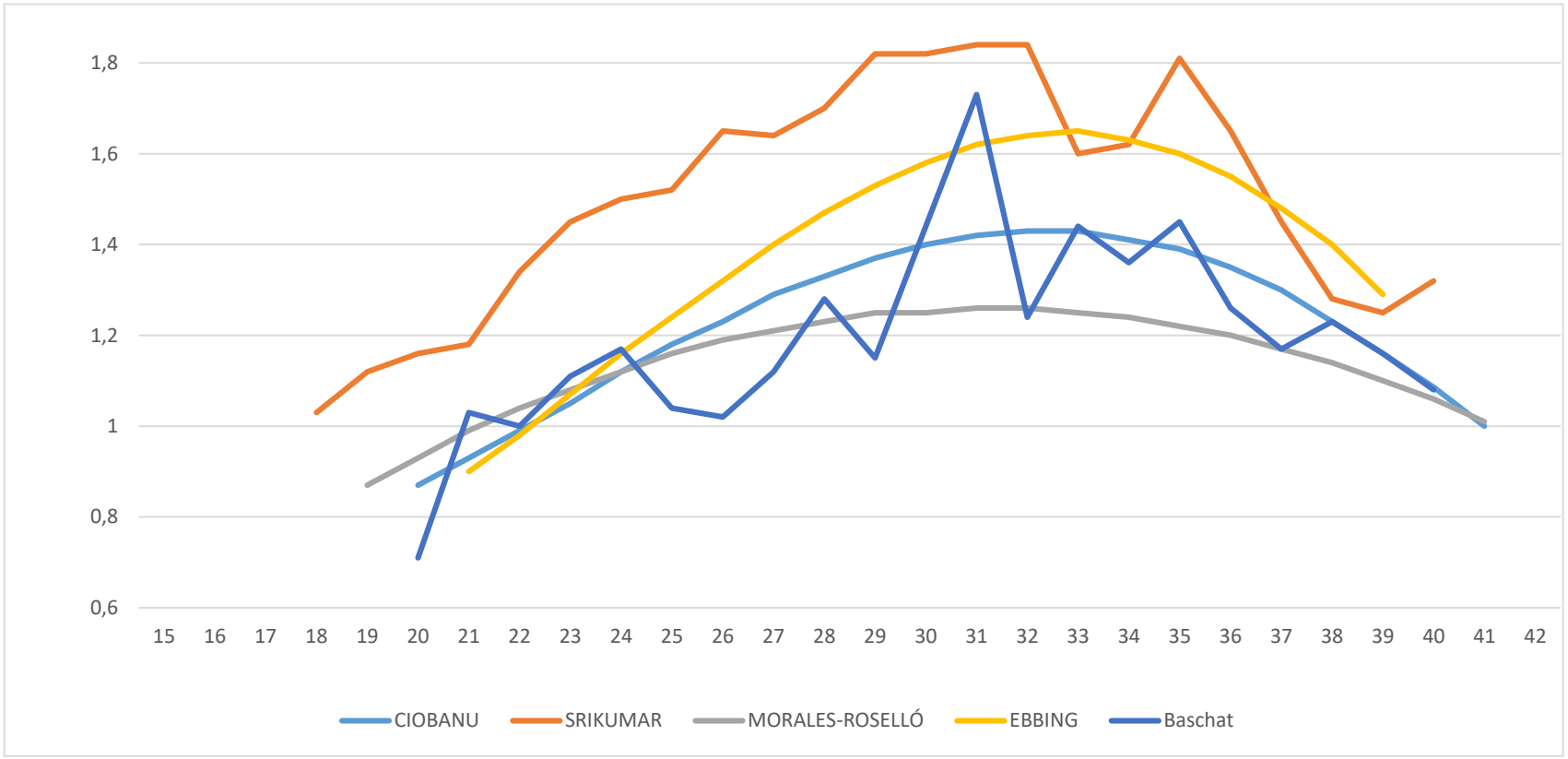


Figure 20. Pulsatility index below the 5th percentile of the most cited cerebroplacental ratio reference standards throughout the pregnancy.

Differences between the highest and lowest published PI values for each week of gestation for the UA within the 95th percentile and MCA and CPR within the 5th percentiles are expressed as percentages and are shown in Figure 21.

The mean between the difference of the highest and lowest PIs for the UA within the 95th percentile for each complete gestational age was 28.02% (range: 21–41%). These differences were much more marked in the case of the highest and lowest PIs for each gestational week for the MCA within the 5th percentile, with a mean difference of 36.86% (range: 26.8–51.3%).

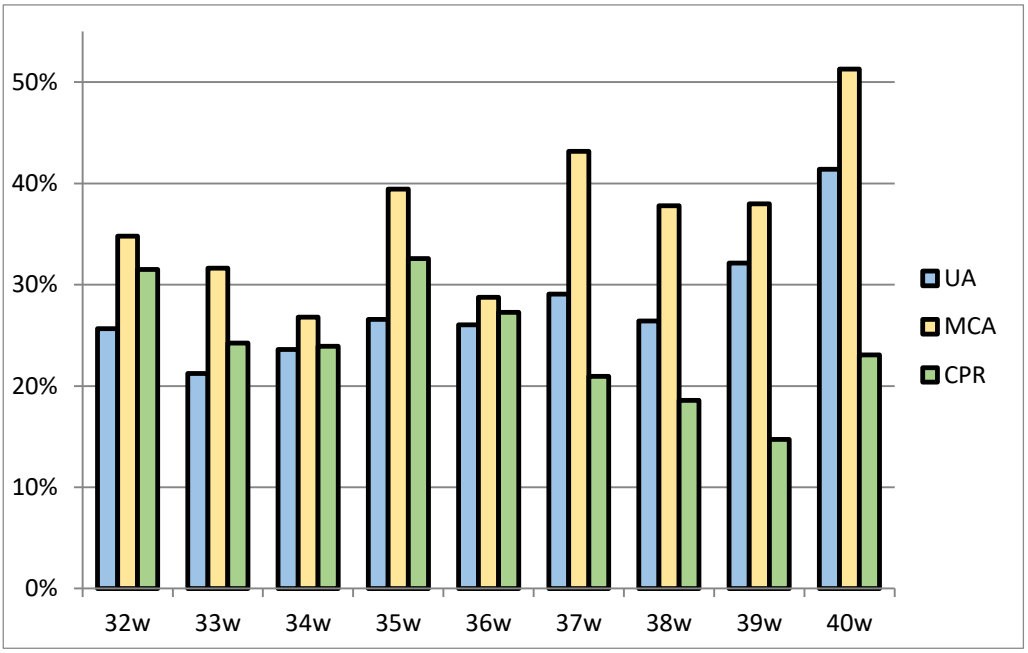


Figure 21. Differences between the highest and lowest pulsatility indices for UA>95th percentile, MCA<5th, and CPR<5th percentiles for each gestational age.

These differences increased after 35 weeks of gestation, where the presence of an abnormal PI for the MCA involves important modifications for clinical management. Finally, PIs for CPR presented the lowest variability, with a mean difference of 24.09% (range: 15–32.6%). However, as expected, the highest PI variability for CPR was again at term.

To evaluate the potential impact of this variability among Doppler PI cut-offs on clinical management, simulation analysis of a historical cohort of 617 consecutive SGA foetuses was performed (Table 14). Depending on the choice of the lowest or highest PIs for the UA greater than the 95th percentile and MCA and CPR less than the 5th percentiles for each gestational age, the proportions of SGA foetuses classified as abnormal according to Doppler PIs for the UA, MCA, and CPR varied from 24.5–2.1%, 0.9–23.1%, and 5.5–33.1%, respectively. According to several clinical guidelines,[4,5] induction of labour may be required for PI values of the UA>95th centile, MCA<5th, or CPR<5th centiles at full term. Even following the same clinical protocol, the potential number of labour inductions for SGA foetuses at term could vary from 33.7–2.1%, 1.1–13.3%, and 5.6–23.3% depending on the PI cut-off variability of the UA, MCA, and CPR, respectively

	Number of SGA foetuses with abnormal Doppler	
Umbilical Artery PI	**Lowest UA>95 (%)**	**Highest UA>95 (%)**
Total SGA* (n=617)	151 (24.5%)	13 (2.1%)
SGA>37 weeks (N=90)	32 (33.7%)	2 (2.1%)
Middle Cerebral Artery PI	**Lowest MCA<5 (%)**	**Highest MCA<5 (%)**
Total SGA* (n=585)	5 (0.9%)	135 (23.1%)
SGA>37 weeks (n=90)	1 (1.1%)	12 (13.3%)
Cerebroplacental Ratio	**Lowest CPR<5 (%)**	**Highest CPR<5 (%)**
Total SGA* (n=577)	32 (5.5%)	191 (33.1%)
SGA>37 weeks (n=90)	5 (5.6%)	21 (23.3%)

Table 14. Number of small-for-gestational-age (SGA) foetuses classified as abnormal Pulsatility Indices for UA, MCA, and CPR by the maximum and minimum published cut-off values for each gestational age. (Simulation from a cohort of 617 consecutive SGA foetuses) * SGA foetuses from 24 to 41 weeks.

5.3. PROJECT 3: DOPPLER STANDARIZATION

In order to aware the scientific society of the importance of research bias and offer a solution to the problem of heterogeneity in fetal Doppler, the FETHUS project has been designed. It is a longitudinal and descriptive prospective study of high methodological quality, to establish universal reference values of fetal Doppler.

5.3.1. RE: ISUOG PRACTICE GUIDELINES ON ULTRASOUND ASSESSMENT TO FETAL BIOMETRY AND GROWTH: TIME TO PAY ATTENTION TO BIAS IN DOPPLER STUDIES.

Ruiz-Martinez S, Oros D. Re: ISUOG Practice Guidelines on ultrasound assessment of fetal biometry and growth: Time to pay attention to bias in Doppler studies. Ultrasound Obstet Gynecol. 2019 Sep;54(3):419. doi: 10.1002/uog.20405.

Estado: Publicado
Factor de impacto: 5.65
Primer cuartil

We congratulate ISUOG's clinical standards committee on the recent publication of the *Practice Guideline and Consensus Statement for ultrasound assessment of fetal biometry and growth*. (124)

They should be commended on what is an important piece of evidence gathering and interpretation. This work is intricately linked with the attempt to determine an international definition of FGR (18).

Given the fact that determining growth potential has not been possible yet, agreeing a clinically useful definition was an overdue first step to homogenised clinical practice; this work will should also assist future research projects and the comparison of different studies.

The performance and interpretation of fetal biometry is the most important component in the diagnosis and monitoring of poor fetal growth. Reliable ultrasound charts are necessary for the prenatal assessment of fetal growth restriction. Considerable methodological heterogeneity with high risk of bias in ultrasound studies aimed at creating charts of fetal size has been previously reported (56). We therefore agree with

the ISUOG Practice Guidelines (124) which, for the first time, recommends the use of *prescriptive* standards of growth as the best strategy to avoid methodological bias; and also recommends comprehensive quality control.

It is time now to pay attention to methodological quality of Doppler. Alongside fetal biometry, assessment of the placental and fetal circulation is the basis for the diagnosis and management of fetal growth restriction. When abnormalities are severe, such as absence or reversed frequencies in the umbilical artery, the evidence is relatively clear. However, in late or mild growth restriction subtler fetal haemodynamic progression is seen, such as elevated impedance to flow in the umbilical arteries; or brain sparing, detected by means of an abnormal cerebroplacental ratio or middle cerebral artery Doppler. Although these are associated with adverse outcome (39), uncertainties remain around their clinical value in decision making, and potential associated long-term consequences. This lack of evidence may be at least partially explained by the considerable methodological heterogeneity in studies reporting reference ranges for UA and MCA Doppler indices and CPR, as shown recently in a systematic review. Methodological limitations in studies on which we base our decisions have been poorly evaluated in the past. Inaccurate definitions and bias can lead to a misinterpretation of clinical evidence, mistaken diagnosis and incorrect management of patients. In our view, the use of Doppler for clinical and research purposes in late or mild growth restriction must to be accompanied by similar strategies to those previously applied in fetal biometry charts - by producing standards and reducing the risk of bias. Thus, developing methodologically appropriate Doppler reference tables and including concrete recommendations on the selection of the best Doppler reference standards in practice guidelines, are urgently needed. Not all questions in nature have answers. It is possible that our lack of knowledge in certain fields is simply due to the fact that answers are not there, and we should accept this with modesty. However, we should not tolerate the ineffectiveness of clinical decision making due to biases, methodological errors or absence of consensus on basic issues.

5.3.2. FETHUS PROJECT

International prescriptive fetal brain Doppler standards (FETHUS project): study protocol. Ruiz-Martinez S, Staines-Urias E, Abadia N, Conde-Agudelo A, Villar J, Delgado JL, Burgos J, Stirnemann J, Parra-Cordero M, Arduini D, Acharya G, Paules C, Papageorghiou AT, Oros D and the FETHUS Consortium.

a. OBJECTIVES:

- **Primary objective**

To develop methodologically robust and prescriptive umbilical artery (UA), middle cerebral artery (MCA) Doppler and cerebroplacental ratio (CPR) standards for practical clinical applications as an international benchmark for the assessment of fetal brain Doppler.

- **Secondary objectives**

a. To examine the effect of maternal and fetal physiological variables at the time of ultrasound, such as the maternal body mass index, fetal and neonatal weight, sex, placental weight and fetal heart rate, on the fetal brain Doppler indexes.

b. To develop a standardized protocol to assess the image quality and the reliability of the middle cerebral artery (MCA) and the umbilical artery (UA) Doppler.

b. MATERIAL AND METHODS

- **Study design**

This is a multicentre, international and prospective longitudinal cohort study. The study will be carried out simultaneously, in the Obstetrics Departments of the Hospital Clinico Universitario (Zaragoza, Spain), Hospital Universitario Virgen de la Arrixaca (Murcia,Spain), Hospital Universitario de Cruces (Bilbao, Spain), St. George's Hospital (London, United Kingdom), Hôpital Necker-enfants maladades (Paris, France), Hospital

Universitario de Chile (Santiago, Chile), Casa di Cura Santa Famiglia (Rome, Italy) and Karolinska University Hospital. (Stockholm, Sweden).

- **Study participants**

In accordance with the prescriptive and high methodological quality approach, inclusion criteria and definitions meet with those previously published by the INTERGROWTH-21st Project.(125)

Included centres should have an adequate clinical infrastructure in a healthy environment and they must meet the following conditions:

1. Reference hospitals controlling all pregnancies of a health area.
2. Hospitals with a Neonatal intensive care unit.
3. Hospitals with a Fetal medicine unit
4. Located at an altitude below 1600 meters.
5. Perinatal mortality <20/1000 live born.
6. Mothers attending antenatal care in these institutions should plan to deliver in that hospital
7. Lac of known non-microbiological contamination such as pollution, radiation or any other toxic substances

Only healthy low-risk pregnant women with adequate obstetric control, with an evolution of pregnancy without complications and in ideal healthy environment meet with inclusion criteria. Participants must meet the characteristics described in table 15:

Baseline maternal characteristics
Written informed consent for participation in the study
Written informed consent for participation in the study
Singleton pregnancy
Aged ≥18 and <35 years
BMI ≥18.5 and <30 kg/m2
Height ≥ 153 cm
No evidence of socio-economic constraints likely to impede fetal growth identified (using local definitions of social risk)
Personal and gestational history
No relevant past medical history, with no need for long-term medication (excluding routine iron, folate, calcium, iodine or multivitamin supplements)
No more than one miscarriage in the two previous consecutive pregnancies
No previous baby delivered preterm (<37+0 weeks of gestation) or with a birthweight <2500 g or >4500 g.
No previous neonatal or fetal death, previous baby with any congenital malformations, and no evidence in present pregnancy of congenital disease or fetal anomaly.
No previous pregnancy affected by pre-eclampsia/eclampsia, HELLP syndrome or a related pregnancy-associated condition.
Evolution of the pregnancy
Natural conception
LMP adjusted by ultrasound with crown–rump length (CRL), between 9 weeks and 0 days and 13 weeks and 6 days
Normal second trimester ultrasound scan.
No use of tobacco or recreational drugs such as cannabis in the 3 months before becoming pregnant
No alcohol use during pregnancy
No clinically significant atypical red cell alloantibodies.
Systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg.

Haemoglobin >10 mg/dl at booking
No clinical evidence of any other sexually transmitted diseases.
Not in an occupation with risk of exposure to chemicals or toxic substances, or very physically demanding activity to be evaluated by local standards. Women should not be conducting vigorous or contact sports, such as scuba diving or similar activities.

Table 15. Inclusion criteria

- **Exclusion Criteria**

The participant may not enter the study if any of the following apply:

1. Suspected congenital malformations, genetic syndromes and/or infections
2. Planned delivery in other institution.
3. Risk of developing severe fetal anaemia.

- **Discontinuation/Withdrawal of participants from Study**

Each participant has the right to withdraw from the study at any time. In addition, the principal investigators from each centre may discontinue a participant from the study at any time when considered in case of:

1. Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
2. Significant protocol deviation
3. Withdrawal of consent
4. Loss to follow up

- **Sample size estimation**

Sample size is one of the most important factors determining the precision of normal reference ranges. The accuracy of estimated centiles is inherently variable; extreme centiles (e.g. 5^{th}, and 95^{th} centiles) exhibit large imprecision because there are, by definition, few observations at extremes of the distribution, while the median has the

greatest precision. Thus, to estimate extreme centiles with great precision, a large total sample size is required(126). According to the literature(108)(127)(128), a longitudinal design has greater efficiency and power than a cross-sectional design for the estimation of references ranges through pregnancy. A longitudinal study allows estimating the variability of Doppler variables between fetuses, and more accurately portraying the hemodynamic pattern over time for the population. Therefore, to estimate the 5^{th} and 95^{th} centiles with the same precision, a longitudinal study would require approximately half to one third the sample size of a cross-sectional study.(129)

In a longitudinal study, the effective sample size depends not only on the number of individuals in the study but also on the number of repeated measurements per individual, whether the measurements are taken in replicate, the method used for curve fitting and smoothing, and the timing of the measurements(14,15). Following previous recommendations(130) for longitudinal ultrasound estimation of variables through gestation, a total of 4000 ultrasound scans are required to reach a maximum precision of 0.02 standard deviations for the 5th and 95th percentiles. An increase in the number of explorations it would increase the cost, time, and manpower without increasing the precision of the results. According to other similar previous studies(60), each patient will have a maximum of 5 Doppler ultrasounds scans, at the time of inclusion at 20 weeks and every 5 weeks until delivery. Therefore, we expect a rate of loss or withdrawal of around 20% of the patients initially recruited, so an initial recruitment of 125 patients is required in each of the 8 centers involved (a total of 1000 patients and 5000 Doppler ultrasound scans) to achieve the proposed objectives. The chosen sample size is larger than most previous studies.

- **Study protocol**

  - **Follow up schedule**

Every pregnant meeting the inclusion criteria will be invited to participate in our study immediately after the routine second trimester US scan. If consents, an appointment for the research US scans will be programme every 5 weeks. All the included centres will initiate the recruitment simultaneously. Twelve to thirteen patients per week will be recruited during ten consecutive weeks. As the study requires enough and similar

number of patients through every week of gestation from inclusion to delivery, study visits will be scheduled according to 5 weekly patterns (Table 16). Each patient will have a maximum of 4 scheduled visits, in addition to their routine gestational control.

Weeks of gestation				
A	22	27	32	37
B	23	28	33	38
C	24	29	34	39
D	25	30	35	40
E	26	31	36	41

Table 16. Follow up scheme

As described in figure 22, the collection of information will be carried out for 31 consecutive weeks or until all the pregnancies included finished in order to collect the variables related to the perinatal outcome.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
A1	20		x					x					x					x													
B1		20			x					x					x					x											
C1			20				x					x					x					x									
D1				20					x					x					x					x							
E1					20						x					x					x				x						
A2						20		x					x					x					x								
B2							20			x					x					x					x						
C2								20				x					x					x				x					
D2									20					x					x					x					x		
E2										20						x					x					x					x
	13R	13R	13R+12	13R	13R+12	12R	12R+13	12R+25	12R+13	12R+25	13	25	25	25	25	25	25	25	25	25	25	25	12	25	12	25	12		12		12

Figure 22: Example of Follow up protocol for each centre. First row weeks of work. Recruitment at 20 weeks and visit every 5 weeks (R=recruitment)

- **Exploration protocol**

All the exams will be carried out by skilled personal with experience in fetal medicine according to the standard methodology. In case of any anomaly would be, it will proceed immediately according to the usual clinical protocols. The detailed measurement protocols, including graphical displays of measurement techniques, and the unique standardization procedures for all measurements been reported elsewhere.(131)
We will collect information on maternal history and evolution of pregnancy at inclusion and follow up controls. At each visit, maternal weight, heart rate and blood pressure(132), as well as a basic ultrasound scan including fetal heart rate and amniotic fluid(133) fetal head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL) will be performed.(60) Umbilical artery (UA) and Middle cerebral artery (MCA) Pulsatility Index (PI), Resistance Index (RI) and Systole/Diastole (S/D) will be measured three times from three separately obtained ultrasound images.(61) Once the pregnancy finish, we will complete the perinatal result from the usual clinical records.

c. OUTCOMES AND CONTROL VARIABLES

- **Main outcomes**
  1. Umbilical artery Doppler (AU); continuous. Pulsatility Index (PI), Resistance Index (RI), Systole/Diastole (S/D) (61)
  2. Middle cerebral artery Doppler (MCA); continuous. Pulsatility Index (PI), Resistance Index (RI), Systole / Diastole (S/D). Maximum systolic velocity (S/D)(61) (REF)
  3. Cerebroplacental ratio (CPR); continuous. (61)

- **Secondary outcomes**
  1. Fetal growth restriction(18); Binary (Yes / No)
  2. Preeclampsia(134); Binary (Yes / No)
  3. Severe preeclampsia(134);Binary (Yes / No)

4. Preterm delivery before 37 weeks of gestation; Binary (Yes / No)
5. Emergency caesarean section due to fetal distress; Binary (Yes / No)
6. Neonatal acidosis (arterial pH <7.10 + EB> 12mEq / L); Binary (Yes / No)
7. Perinatal mortality (> 22 weeks of gestation - <28 days postpartum); Binary (Yes / No)
8. Neonatal Intensive Care Unit admission; Continuous (days)
9. Significant neonatal morbidity (convulsions, intraventricular haemorrhage> grade III, periventricular leukomalacia, hypoxic-ischemic encephalopathy, abnormal electroencephalogram, necrotising enterocolitis, acute renal failure (serum creatinine> 1.5 mg / dL) or cardiac failure (requiring inotropic agents); Binary
10. Perinatal mortality; Binary (Yes / No)

- **Control variables**

- Maternal age at birth; Continuous (years)
- Smoking during pregnancy; Continuous (cigarettes / day)
- Maternal weight at the booking; Continuous (Kg)
- Maternal height; Continuous (cm)
- Maternal ethnic origin; categorical (Europe, Africa, South America, Maghreb, Asia, Other)
- Parity (number of deliveries> 22 weeks); Discrete
- Previous preeclampsia; Binary (Yes / No)(134)
- Previous gestational hypertension; Binary (Yes / No) (134)
- Previous growth restricted fetuses (neonatal weight <10th percentile); Binary (Yes / No)(18,59)
- Diastolic blood pressure; Continuous (mmHg)(134)
- Systolic blood pressure; Continuous (mmHg) (134)
- Maternal heart rate; Continuous
- Fetal heart rate; Continuous
- Biparietal diameter; Continuous (mm) (60)
- Head Circumference; Continuous (mm) (60)

- Abdominal circumference; Continuous (mm(60)
- Femur length; Continuous (mm) (60)
- Estimated fetal weight; Continuous (mg) (24)
- Deepest amniotic fluid pocket; Continuous (mm)(133)
- Gestational age at inclusion; Continuous (days)
- Last menstrual period (dated by ultrasound <14 weeks according to CRL(135)); Continuous (days)
- Gestational age at birth; Continuous (days)
- Neonatal weight; Continuous (g)
- UA and MCA Doppler Angle correction; Continuous (grades)
- Ultrasound machine and probe; used in the scan; discrete (names)

d. QUALITY CONTROL

We will carry out a strict quality control, following the recommendations previously published by our group (136). Ultrasound machines will be equipped with real-time, grayscale, two-dimensional (2D) transducers, and have adjustable and displayed output power, freeze frame and zoom options as well as electronic calipers. Doppler ultrasound measurements will be recorded using a 2–5, 4–8 or 2–7-MHz transabdominal transducer. All the images will be storage, scored and reviewed following quality criteria(136)(137), to monitor validity and reliability, and continuous assessment of all data collected. To assess the intra and interobserver variability, an external expert in fetal Doppler will assess ten images of each sonographer, and ten randomized patients of each centre will be scanned by all the sonographers. Scans will be performed by a limited number of experienced and specifically trained sonographers in each centre. Angle correction will be always clearly specified and at we will take least three Doppler measurements per fetus per scan. Sonographers will be blinded to Doppler measurements during the US scan, unless clinical reasons recommended to unmask.

e. STATISTICAL ANALYSIS

Statistical management will be carried out according to previously described methodology(130) with the objective of establishing prescriptive normal standards for the MCA, UA and CPR Doppler. It is desirable to be able to use all the data from the eight study sites to provide a single global standard for each measurement and to give the strongest basis for the construction of Doppler curves for international clinical applications. However, it is important to be satisfied that the data from the different centres are similar enough to be combined. The appropriateness of pooling data from all sites to construct UA, MCA and CPR standards will be assessed by comparing site means, standard deviations and the fitted centiles from the analysis of each site to the corresponding values from analyses of data from all sites combined. A difference of > 0.5 SD between the values for an individual site and the pooled sample will be used as a pre-set trigger for considering whether to adjust by site for the purposes of pooling data. We will conduct sensitivity analyses exploring the effect of removing each of the populations in turn on the pooled mean at different gestational ages and the estimated regression models.

We will report the mean and SD of each measurement and sample size for each completed week of gestation. Data will be presented in a scatter diagram Doppler chart including the 5th, 50th and 95th centiles. Reference centiles should change smoothly with gestation, and they should provide a good fit to the raw data. It is desirable for the statistical model to be as simple as compatible with these requirements.(127) Fetal Doppler measures change smoothly and systematically over gestation and have a normal distribution for a given gestational age. We will thus initially apply simpler models, based on fractional polynomial regression functions for the mean and SD of each fetal measurement assuming normality at each gestational age(138), and only move to the more complex models described elsewhere(130) if the fit is inadequate. The distributions of residuals for the fitted centiles for each fetal measurement will be examined both for all sites combined and for each site separately and plotted against the gestational age. The maternal and fetal outcomes will also be analysed through a descriptive analysis in order to describe the sample and exclude those patients in whom an exclusion criterion may appear before or after delivery. Analyses will be performed

using STATA software (StataCorp, College Station, Texas, USA) and R version 3.5 (R foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

f. ETHICS AND SAFETY

This protocol has been approved by the ethic committee of Aragon (REF), the research ethics committees of the individual participating institutions and the corresponding regional health authorities in which the project will be implemented. Exposure to ultrasound should comply with the ALARA ('as low as reasonably achievable') principle(139). The mechanical and the thermal index will be always kept below 1.9 and 1.5 respectively.

No financial compensation will be made to patients who agree to participate. Pregnancy control and delivery assistance will always be attended by experienced personnel, in accordance with international clinical standards. The study will not interfere with any of the centre's care tasks. Information management will always meet with the laws of each one of the involve centres. The fair and dignified treatment of the personal data of every patient included in the study will be guaranteed

.

6. DISCUSSION

With this project we demonstrate, for the first time, the great heterogeneity and the low methodological quality of published studies that establish reference values of fetal doppler. The influence of methodological biases in research is also demonstrated.

In addition, we analyze the great clinical impact of this variability in the management of the IUGR fetus.

Finally, we offer a solution to this problem, presenting the protocol of the FETHUS project, the first study that establishes reference values from a study of high methodological quality

6.1. PROJECT 1: AN OBJECTIVE SCORING METHOD TO EVALUATE IMAGE QUALITY OF MIDDLE CEREBRAL ARTERY DOPPLER

This study demonstrates that there is better interobserver agreement using a 6-point objective scoring system of MCA Doppler images than there is for subjective evaluation.

Objective scoring systems have been validated for use in fetal biometry(63), CRL assessment (140), and NT measurement (141).

MCA Doppler has a proven role in the assessment of small for gestational age fetuses(21,142,143) and also in monitoring fetal anemia(144–146). The potential of MCA in reducing still birth in those contexts makes accurate assessment particularly important.
Quality assurance using objective image scoring and targeted feedback has been shown to improve the consistency of ultrasound measurements even among trained sonographers(58).

We employed an established methodology and devised a 6-point objective scoring method which incorporates technical recommendations from an international guideline for MCA Doppler assessment(61). In addition to high interobserver agreement for the

overall objective score, we demonstrated excellent agreement for most of the individual criteria.

A very low Cronbach- a scores suggest that there is no interdependence between the individual criteria. This can be explained because each individual criterion assesses fundamentally different quality properties of a Doppler image such as the anatomic plane of acquisition or the angle of Doppler application or the features of waveform Doppler optimization. As a result, our score distributions are less skewed and the median score is 4.

Among other strengths of this study are that the sample was randomly drawn from an unselected pregnant population undergoing routine examinations at 36weeks, that is, the gestation where MCA (as part of the CPR) is most useful in assessing placental insufficiency. The sonographers who performed the measurements were appropriately trained sonographers or fellows performing ultrasound examinations within the standards of a tertiary UK NHS service and they were using regularly upgraded scan machines. The study was adequately powered and the use of PABAK is the recommended methodology for assessing image scoring agreement (140).

We also acknowledge some limitations. There was a statistically significant difference of mean score between the two reviewers but the magnitude of this difference was clinically insignificant and did not affect the overall reliability. The scoring cut-off used to define good and poor quality (though consistent with previous image scoring literature) is rather arbitrary. Given the low interdependence between criteria it could be argued that each criterion is absolutely essential for the image to be deemed satisfactory and that the quality threshold should be set higher than 4. However, this does not invalidate the conclusions of this exercise which demonstrates that the scoring method is reliable. It is up to institutions to define the level of threshold in their clinical practice. Another limitation is that these MCA images were taken as part of a universal screening program for fetal growth and CPR but they were not performed specifically for peak systolic velocity measurement. Nevertheless, the same quality principles underlie the latter measurement and it is reasonable to assume that the proposed scoring method is valid when MCA is used as a screening tool for fetal anemia. This

scoring method cannot assess the effect of pressure applied on the ultrasound probe which is known to alter MCA values (147). Image analysis is time-consuming and should not be the sole measure of quality control. However, it is a useful tool as part of a quality control strategy which may also include quantitative analysis of measurement distributions of individual sonographers, similar to those strategies employed for quality assurance of NT programs (141).

6.2. PROJECT 2: DOPPLER REFERENCE RANGES AND CLINICAL IMPACT

This study has shown that there is considerable heterogeneity in the methodological quality of ultrasound studies aimed at creating reference ranges for UA and MCA Doppler indices and CPR and the clinical impact have these differences. These differences may at least partly explain the differences in reported reference ranges and these may in turn explain some of the discrepancies seen in perinatal research based on Doppler, including patterns of Doppler progression(148–151) or even long term outcome(46,152). This review determined the potential risk of bias based on study design and statistical and reporting methods using a predefined quality-scoring sheet of 24 criteria to determine which of these studies were most likely to be relevant for clinical management.

Using clinical information collected routinely to create a reference could be an important source of bias, with over-representation of at-risk cases. Sixteen studies were performed on unselected populations, including pregnancies with suspected IUGR and an unselected population ensures a better representation of the underlying population(153,154).

We consider that the aim of a fetal Doppler chart should be to depict how fetal hemodynamics should be under optimal conditions (a prescriptive standard) rather than how they often are (a descriptive reference)(155).

Three-quarters of the published references were performed by one sonographer and Multi-sonographer studies increase external validity and data consistency can be

achieved by undertaking a formal standardization exercise prior to the start of a study(58).

A lack of blinding of researchers in studies has been shown to bias results(156) and the STROBE guideline recommends blinding in order to reduce such bias(157). The effect of lack of blinding on expected-value bias has also been demonstrated in the field of prenatal ultrasound, although the magnitude of the effect is not well understood. It is suggested that such blinding should be undertaken not only in the research setting when creating ultrasound standards, but also in clinical practice in order to reduce such expected value bias(158,159); this occurred in only one study.

Monitoring of ultrasound data quality through a comprehensive quality control strategy has been proposed as another way to ensure high quality and should ideally include the use of image scoring methods and the assessment of intra- and interobserver variability of measurement(137).

Accurate estimation of gestational age is a fundamental prerequisite for creating any fetal standard(54,160,161). Only 20 studies used dating either by CRL alone or by LMP corroborated by CRL.

Approximately one-third of the studies did not report the results in the form of tables of fitted centile values, gestational age curve charts and regression equations for both the mean and SD(127). Both the median and variance should be modelled as a function of gestational age in a manner that accounts for the increasing variability with gestation and provides smooth centile curves; goodness of fit testing should demonstrate that these curves describe accurately the structure of the raw data(94).

In relation to the clinical impact of these large differences between reference values, it should be noted that, a growing body of evidence suggests that MCA Doppler, alone or in combination with the UA-PI (i.e., CPR), may be helpful in identifying fetuses at risk of IUGR(45,162,163) as a surrogate marker of the redistribution of blood flow for vital

organ prioritization(46). UA-PI, MCA-PI and CPR are now the most widely used tool for control and decision making for SGA fetuses(17,32).
UA-PI vasoconstriction is defined according to a statistical cut-off of the 95th percentile(18). Similarly, the 5th percentile defines brain vasodilation for the MCA-PI or CPR(18). Therefore, appropriate Doppler reference values are needed to accurately estimate these cut-off points.

The top three most cited studies by Arduni(62), Baschat(103), and Acharya(100) showed an important risk of bias due to the fact that they were only the sixth, eleventh, and ninth ranked studies based on methodological quality according tour study. It could be argued that older works are more likely to be cited than more recent studies with higher quality methodology(87) because newer works have not had sufficient time to implant themselves in clinical practice.

As shown in Figures 18, 19, and 20, an irregular distribution was observed among the cut-off values at gestational time points in many of the analysed reference ranges, suggesting inappropriate statistical treatment of the data. We want to highlight the impact of the heterogeneity of the Doppler reference values being used within clinical practice and research.

Simulation analysis performed in a real cohort of SGA fetuses clearly showed that the use of inaccurate tools can lead to inaccurate decision making for important clinical issues. The optimal time for pregnancy completion for SGA fetuses is one of the main focuses of interest in IUGR research.(102)(103)(91) According to our results, even with the use of a standardized clinical protocol, the Doppler reference values used have a significant clinical impact. For example, a rate of induction at term could range from 2.1-33.7% for UA-PI, 1.1- 13.3% for MCA-PI, and 5.6-22.3% in the case of CPR. Notably, the broadest variation among the Doppler reference values is at full term, which is a critical moment to programme different therapeutic actions. From our point of view, this potential variability in the clinical management of SGA fetuses is unacceptable.

Strengths of the study

The main strength of this review lies in the rigorous methodology used, which included:

- The implementation of guidelines for the conduct and reporting of systematic reviews of observational studies;
- The inclusion of a relatively large number of studies in the review and the use of a quality score checklist modified from that used in previous studies(44,54,57), which allowed an objective and quantitative assessment of study methodology.
- The use of a quality score in the form of a percentage allowed an objective rather than empirical assessment of quality, and also enabled regression analyses in order to identify predictors of quality or other trends.

Potential limitations of the study

- The inclusion of studies published in only the English or Spanish language. It is possible that eligible studies published in other languages may have been missed. Nevertheless, this restriction is unlikely to be a significant limitation because the top-cited Doppler reference value charts were always published in English, as expected. Additionally, the literature search did not have restrictions for year of publication because some of the older ultrasound Doppler studies are still used in current clinical practice.

- It may be possible that biological variation might account for differences in Doppler results. For example, Doppler parameters obtained at a very high altitude(165) (166) may show some differences from measurements obtained near sea level due to adaptation; thus, reference ranges obtained at a very high altitude may not be appropriate to be considered normal ranges, in the same way as study sites at high altitude were excluded when creating fetal growth standards(55). In addition, most Doppler territories, but in particular those of the MCA, show dynamic changes related to fetal movements, breathing or applied pressure from the ultrasound probe; however, while these changes can have an effect on an individual fetus, in studies

creating ranges, these should not lead to bias unless standard guidelines were not followed.

- The reviewers who performed the data abstraction were not blinded to the origin and authors of the included studies.

- The evaluation of the impact of Doppler reference value charts in clinical management was performed in a retrospective cohort of SGA foetuses controlled with specific Doppler references. Thus, our results could be potentially biased. Due to the high number of published Doppler value reference charts, it is unlikely that a prospective study with a similar aim was conducted.

- Apart from the PI, other parameters such as systolic/diastolic ratio (S/D) are sometimes used for the management SGA fetuses. We did not include this analysis for two reasons: firstly, only three of the most cited published Doppler references (Ayoola(88)50, Acharya(100)36 and Fogarty(120)42) give reference ranges for the umbilical artery S/D ratio, and one (Tarzamni(93)) mention the middle cerebral artery S/D ratio. Secondly, as we did not have data on the S/D ratio from the cohort of SGA fetuses that we used to perform the simulation analysis, this could not be included here. Although this is a potential limitation the relationship between PI, RI, S/D ratios mean that the principle, of reaching different clinical decisions depending on the reference chart used, still applies.

6.3. PROJECT 3: DOPPLER STANDARIZATION

Reliable Doppler references ranges are necessary for the assessment fetal well-being. The lack of evidence may be at least partially explained by different Doppler references used to define normal or abnormal findings.

Our previous study reports a systematic review showing considerable methodological heterogeneity and high risk of bias based on study design and statistical and reporting methods in studies reporting reference ranges for UA and MCA Doppler indices and CPR, with important implications for clinical practice. Selection of methodologically biased Doppler reference values can result in significant variability in the management of FRG, that may lead to misinterpretation of clinical evidence, mistaken diagnosis, incorrect management of patients and inaccurate research conclusions. The goal of any Doppler-triggered management protocol is to improve perinatal mortality and morbidity. Early antenatal detection, treatment where appropriate, and timely delivery could minimise the risks significantly. But an unnecessary early intervention may result in excess morbidity from prematurity and considerable anxiety in families and clinicians, whilst a delay may result in a stillbirth or severely compromised newborn.(13)

Standardization of methodologies for Doppler velocimetry and developing methodologically appropriate Doppler reference ranges which can be correctly interpreted and applied in clinical practice, are urgently needed. Thus, our aim is to develop methodologically robust Doppler reference standards according to a set of quality recommendations(55,137), for practical clinical applications as an international benchmark for the assessment of fetal brain Doppler.

7. CONCLUSSIONS

- After performing MCA image quality control, we propose an objective scoring system to assess MCA Doppler measurement quality. Providers should use this regularly to audit the performance of individual sonographers in their institutions; and should decide locally the satisfactory score threshold in order to determine the need for feedback and retraining.

- Our systematic review has identified many ultrasound studies with poor methodology and reporting of reference ranges for UA and MCA Doppler indices and CPR. These should be taken into account in future studies and we recommend using a checklist of methodological good practices in further studies aimed at creating reference ranges for UA and MCA Doppler parameters and CPR; the criteria listed under low risk of bias would constitute the optimal methodological aspects for any future study.

- The selection of the Doppler reference values determines the significant variability in the clinical management of IUGR fetuses that may lead to suboptimal outcomes and inaccurate research conclusions.

- As a result of our studies, we consider that an attempt to standardize fetal Doppler reference ranges is mandatory. For this reason, we propose the FETHUS project, an international prospective study with great methodological quality

- Después de realizar un control de calidad de imágenes de ACM, proponemos un sistema de puntuación objetivo para evaluar la calidad de medición Doppler ACM. Se debería utilizar este sistema para auditar la calidad de los ecografistas de forma individual en sus instituciones; decidiendo en cada centro la puntuación mínima satisfactoria para determinar la necesidad de mejora y entrenamiento.

- Nuestra revisión sistemática ha identificado muchos estudios de Doppler fetal con metodología deficiente que establecen rangos de referencia para los índices Doppler UA y MCA y RCP. Esto debe tenerse en cuenta en futuros estudios y para ello, recomendamos utilizar una lista de verificación de buenas prácticas metodológicas en estudios posteriores destinados a crear rangos de referencia para los índices Doppler de AU, ACM e ICP; los criterios considerados de bajo riesgo de sesgo constituirían los aspectos metodológicos óptimos que deberían cumplir cualquier estudio futuro.

- La selección de los valores de referencia Doppler determina una variabilidad significativa en el manejo clínico de los fetos CIR que puede conducir a resultados subóptimos y conclusiones en investigación inexactas.

- Como resultado de nuestros estudios, consideramos que es necesario estandarizar los rangos de referencia de Doppler fetal. Por este motivo, proponemos el proyecto FETHUS, un estudio prospectivo internacional con gran calidad metodológica.

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9.APPENDIX

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ORIGINAL ARTICLE

An objective scoring method to evaluate image quality of middle cerebral artery Doppler

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ABSTRACT

Objective: To validate an objective scoring system for middle cerebral artery (MCA) pulsed wave Doppler images.

Method: From an image database of routine 36-week scans, a random sample of MCA Doppler images was selected. Two reviewers rated the images subjectively as acceptable or unacceptable. Subsequently they used an objective 6-point image scoring system and awarded one point for each of the following: (1) anatomical site, (2) magnification, (3) angle of insonation, (4) image clarity, (5) sweep speed adjustment, and (6) velocity scale and baseline adjustment. Image scores 4–6 were defined as good quality whereas 0–3 as poor. The subjective and objective agreement between the two reviewers was compared using the adjusted Kappa statistic.

Results: A total of 124 images were assessed. Using objective scoring the agreement rate between reviewers increased to 91.9% ($\kappa = 0.839$) compared to subjective agreement 75.8% ($\kappa = 0.516$). The agreement for each criterion was: anatomical site 91.1% ($\kappa = 0.823$), magnification 95.2% ($\kappa = 0.903$), clarity 83.9% ($\kappa = 0.677$), angle 96.0% ($\kappa = 0.919$), sweep speed 98.4% ($\kappa = 0.968$), and velocity scale and baseline 94.4% ($\kappa = 0.887$).

Conclusion: Objective assessment of MCA Doppler images using a 6-point scoring system has greater interobserver agreement than subjective assessment and could be used for MCA Doppler quality assurance.

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Agreement; Doppler; image scoring; middle cerebral artery; quality; reliability; reproducibility

Introduction

Doppler assessment of the middle cerebral artery (MCA) is receiving increasing attention in research and clinical practice. The cerebroplacental ratio (CPR) has become part of the assessment of small for gestational age and potentially compromised fetus [1,2]. It may also form part of the more difficult but potentially more useful task of identifying the "growth restricted" but appropriate for gestational age fetus [3]. A number of studies have correlated the MCA and particularly the CPR with adverse perinatal outcomes, although its role in clinical decision-making remains less clear. It is also an essential part of the assessment of the potentially anemic fetus, most commonly in the evaluation of pregnancies exposed to red cell antibodies [4] or parvovirus [5]. In this role its usage can dictate the need and timing of intrauterine transfusion and can prevent unnecessary invasive fetal assessment.

Doppler ultrasonography is a safe and noninvasive technique commonly used in fetal monitoring [6]. Like other medical techniques, it requires learning and training. The measurement of the MCA must follow standards so that the values obtained are adequate and reproducible in order to maximize the potential of Doppler assessment in clinical practice. Objective scoring has been shown to be useful for fetal biometry [7] and crown-rump length (CRL) [8]. For nuchal translucency (NT) for instance, it is known that appropriate feedback and intervention for individual sonographers may improve their performance [9]. Guidelines describe the correct Doppler assessment of the MCA [10] but there are no published studies objectively assessing its key criteria and no scoring method for assessing whether an MCA Doppler image has been recorded accurately.

The aim of this study is to evaluate an objective scoring system for MCA Doppler images and to compare this with subjective assessment.

Materials and methods

This is an ultrasound image scoring reliability study. All pregnant women in the John Radcliffe Hospital,

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Table 1. Image scoring criteria for MCA Doppler image.

Criterion	Description
Anatomical site	Axial brain section visualizing the thalami and sphenoid wings and identifying the circle of Willis by color Doppler with the gate placed in the proximal third of the MCA
Magnification	MCA image occupies at least 50% of the screen
Image clarity	Waveform should be clear without artifacts and tracing should be accurate
Angle of insonation	Less than 15° followed by angle correction as close as possible to 0°
Sweep speed adjustment	3–10 uniform waveforms are visualized
Velocity scale and baseline adjustment	Waveforms occupy 75% of the screen

Oxford, United Kingdom are offered MCA Doppler assessment as part of routine growth scan at 36-week gestation. Around 1270 examinations were performed between December 2016 and January 2017 and a random 10% sample was selected. All images were taken by four different trained sonographers, following the same institutional protocol and using two different machines (Phillips Epiq 7 and GE Voluson E8). According to a previously published power calculation, a sample of 125 examinations is adequate to detect a 10% difference between two reviewers with 90% power, assuming a rate of interobserver agreement of 80% [7]. The current study is covered by ethics reference REC 17/SC/0374 granted on 27 July 2017; patient informed consent is not required as this is a retrospective review of routinely collected data.

An objective scoring system was developed based on the ISUOG Practice Guidelines [10]. The following six criteria (Table 1) were defined: (1) anatomical site, 2) magnification, (3) image clarity, (4) angle of insonation, (5) sweep speed adjustment, and (6) velocity scale and baseline adjustment. Once these features are fulfilled, the pulsatility index, resistance index, and peak systolic velocity are obtained automatically from at least three uniform waves.

Two assessors were blinded to each other's rating results and they rated all images subjectively as "acceptable" or "unacceptable." To assess the images objectively, the same two assessors used the 6-point image scoring system. One point was awarded for each criterion satisfied; and zero if the criterion was not satisfied (Figure 1). All criteria were accorded equal weight and the sum of points was the final score. We considered images scoring four or more points as good quality; and those scoring less than four points as poor quality.

Score distributions were compared between the two observers using the Wilcoxon test. Subjective and objective agreement between observers was assessed using the unadjusted (Cohen) and the prevalence-adjusted and bias-adjusted (PABAK) Kappa statistics [11]. Interitem consistency of the six criteria of the scoring system was assessed for each observer using the Cronbach's alpha statistic [12]. Analyses were performed using IBM SPSS statistics version 23.

Results

A total of 124 MCA Doppler images from four sonographers were used. Using subjective scoring, reviewers A and B judged 71 (57.3%) and 79 (63.7%) images, respectively, to be acceptable. About 60 (48.4%) images were acceptable by both assessors whereas 34 (27.4%) were unacceptable by both, an agreement rate of 75.8%.

The distribution of objective scores among subjectively rated images is shown in Table 2. Images deemed subjectively acceptable would unsurprisingly have an objective score most often 4–6 and never 1–2. Conversely images deemed unacceptable would usually have an objective score 1–3, but it is interesting to note that 10–20% of those images could have an objective score of 4–6.

Using the objective scoring method the agreement rate between reviewers increased to 91.9%, adjusted $\kappa = 0.839$ compared to subjective rating agreement 75.8%, adjusted $\kappa = 0.516$ (Table 3). Both reviewers had a median score of four (range 1–6) and the score distributions are shown in Figure 2. Reviewer A had a mean score 4.27 whereas reviewer B a mean score 4.17 and this small difference was statistically significant (Wilcoxon signed rank $p = .022$).

Table 3 demonstrates that objective assessment of the image quality using the overall image score has the highest reliability between the two reviewers when compared to any other combination of assessment methods. Table 4 highlights that among the individual scoring criteria, highest reliability was noted for the sweep speed adjustment (adjusted $\kappa = 0.968$); and lowest reliability for the criterion of image clarity (adjusted $\kappa = 0.677$).

Criteria interdependency was almost nonexistent as demonstrated by the low or negative Cronbach α-values for each individual criterion (Table 5).

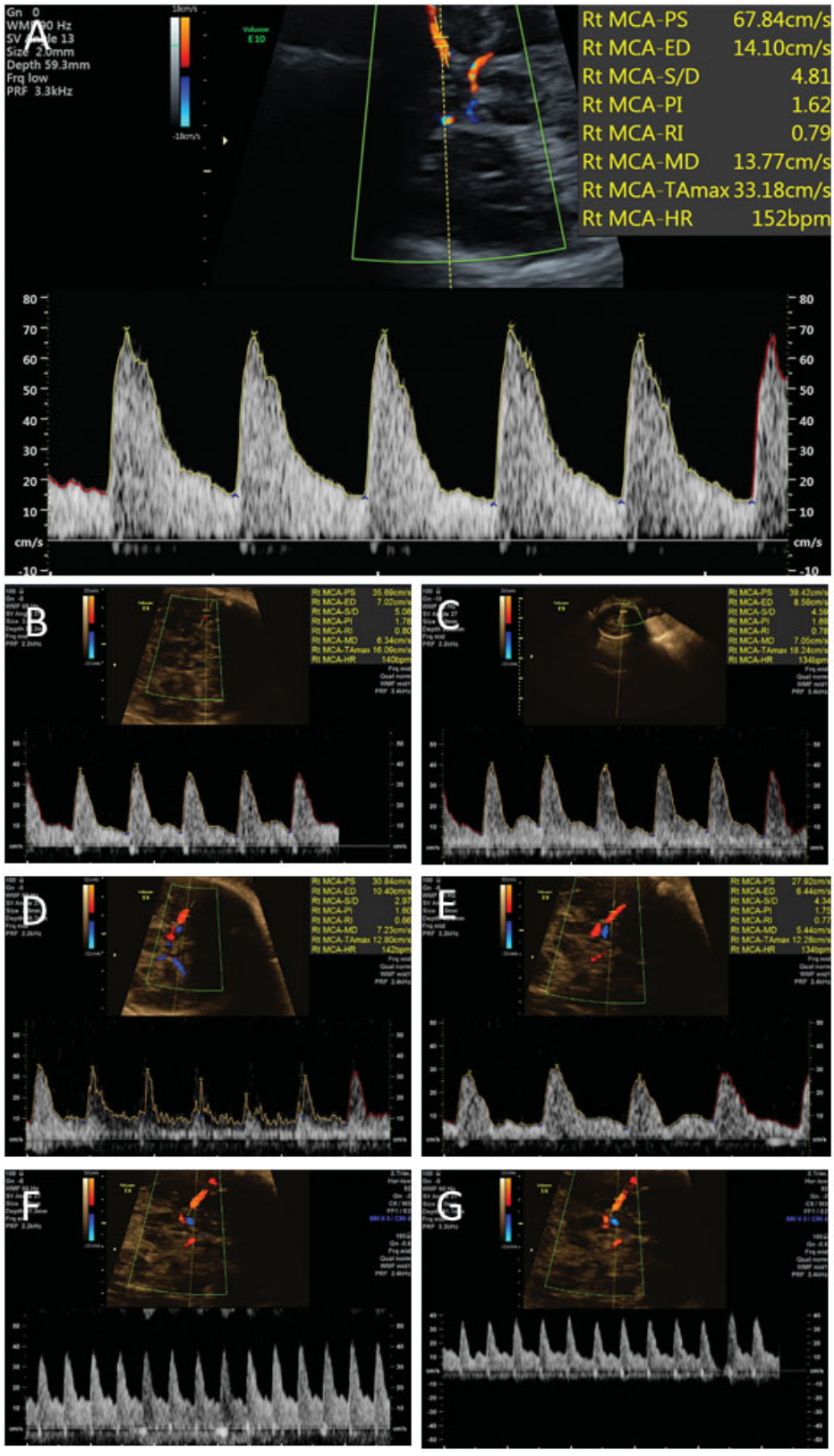

Figure 1. Representative examples of middle cerebral artery (MCA) images (A) where all scoring criteria are met; (B) wrong anatomical site: circle of Willis and MCA poorly identified with gate too lateral and near the skull; (C) inadequate magnification; (D) suboptimal image clarity resulting in inaccurate tracing of the waveform; (E) no angle correction; (F) no sweep speed adjustment resulting in too many waves per image; and (G) no baseline and velocity scale adjustment so that waveform does not fill up the screen.

Table 2. Comparison between subjective assessment and objective scoring for both observers.

	Objective image score					
Subjective assessment	1	2	3	4	5	6
Unacceptable A	1 (1.9%)	11 (20.8%)	15 (28.3%)	15 (28.3%)	10 (18.9%)	1 (1.9%)
Acceptable A	–	–	3 (4.2%)	26 (36.6%)	32 (45.1%)	10 (14.1%)
Unacceptable B	2 (4.4%)	7 (15.6%)	16 (35.6%)	13 (28.9%)	6 (13.3%)	1 (2.2%)
Acceptable B	–	–	5 (6.3%)	21 (26.6%)	37 (46.8%)	16 (20.3%)
Unacceptable by both A and B (objective score A)	1 (2.9%)	11 (32.4%)	10 (29.4%)	10 (29.4%)	2 (5.9%)	–
Unacceptable by both A and B (objective score B)	2 (5.9%)	7 (20.6%)	13 (38.2%)	8 (23.5%)	3 (8.8%)	1 (2.9%)
Acceptable by both A and B (objective score A)	–	–	1 (1.7%)	20 (33.3%)	29 (48.3%)	10 (16.7%)
Acceptable by both A and B (objective score B)	–	–	1 (1.7%)	17 (28.3%)	28 (46.7%)	14 (23.3%)

Table 3. Agreement between subjective assessment and objective scoring for MCA Doppler image.

Criterion	Agreement (%)	Kappa Cohen (95% CI)	Adjusted kappa PABAK (95% CI)
Subjective A/subjective B	75.8	0.496 (0.341–0.651)	0.516 (0.365–0.667)
Subjective A/ objective B	78.2	0.493 (0.334–0.652)	0.565 (0.419–0.710)
Objective A/subjective B	75.0	0.460 (0.311–0.609)	0.500 (0.348–0.652)
Subjective A/objective A	79.8	0.530 (0.375–0.685)	0.597 (0.456–0.738)
Subjective B/objective B	76.6	0.494 (0.347–0.641)	0.532 (0.383–0.681)
Objective A / Objective B	91.9	0.780 (0.651–0.909)	0.839 (0.743–0.935)

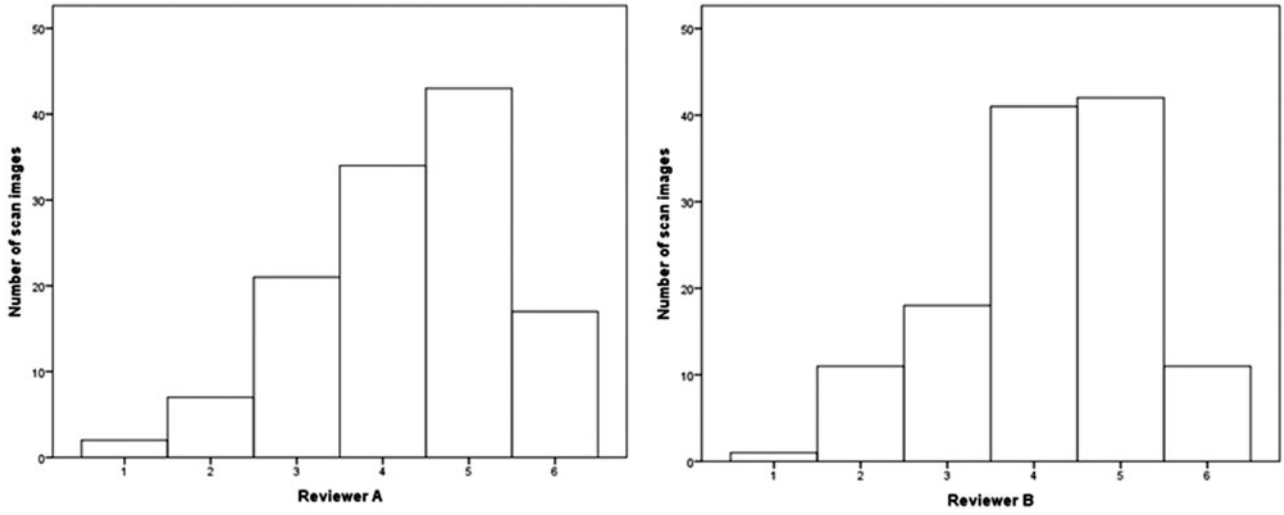

Figure 2. Distribution of total image scores for both reviewers.

Discussion

This study demonstrates that there is better interobserver agreement using a 6-point objective scoring system of MCA Doppler images than there is for subjective evaluation.

It is widely accepted that quality assurance mechanisms should be in place when obstetric ultrasound is used in research or as part of an established screening program [13]. Objective scoring systems have been validated for use in fetal biometry [7], CRL assessment [8], and NT measurement [9]. MCA Doppler has a proven role in the assessment of small for gestational age fetuses [1,2,14] and also in monitoring fetal anemia [4,5,15]. The potential of MCA in reducing still birth in those contexts makes accurate assessment particularly important. Quality assurance using objective image scoring and targeted feedback has been shown to improve the consistency of ultrasound measurements even among trained sonographers [16].

We employed an established methodology and devised a 6-point objective scoring method which incorporates technical recommendations from an international guideline for MCA Doppler assessment [10]. In addition to high interobserver agreement for the overall objective score, we demonstrated excellent agreement for most of the individual criteria. Clearly defined and unequivocally quantifiable criteria—such as scale velocity adjustment—tend to have very high agreement. On the other hand, image clarity—an essential but less quantifiable criterion—demonstrates comparatively lower agreement.

There are some interesting observations when comparing this Doppler-based image quality score to a

Table 4. Agreement between reviewers for each scoring criterion.

Criterion	Agreement (%)	Kappa Cohen (95% CI)	Adjusted kappa PABAK (95% CI)
Anatomic site	91.1	0.783 (0.661–0.905)	0.823 (0.722–0.923)
Magnification	95.2	0.845 (0.725–0.965)	0.903 (0.828–0.979)
Image clarity	83.9	0.644 (0.503–0.785)	0.677 (0.548–0.807)
Angle	96.0	0.917 (0.846–0.988)	0.919 (0.850–0.989)
Sweep speed	98.4	0.849 (0.643–1.000)	0.968 (0.923–1.000)
Velocity and baseline	94.4	0.868 (0.774–0.962)	0.887 (0.806–0.968)

Table 5. Interitem consistency among image scoring criteria for MCA Doppler image.

	Cronbach's α for excluding each item individually	
	Reviewer A	Reviewer B
Anatomic site	0.123	−0.124
Magnification	0.341	0.323
Image clarity	0.118	0.031
Angle	0.269	0.162
Sweep speed	0.246	0.118
Velocity and baseline	0.107	−0.048
All six items	0.243	0.116

previously validated score for CRL measurement [8]. Very low Cronbach α-scores for our scoring method suggest that there is very little or no interdependence between the individual criteria. Higher Cronbach scores were observed for CRL scoring [8] and this suggests higher consistency and interdependence between the individual criteria for CRL, that is, higher likelihood that more than one criterion would score positive for the same underlying reason. As a result, CRL score distributions tend to be positively skewed with median score 6. In our study, very low Cronbach α-scores suggest that there is no interdependence between the individual criteria. This can be explained because each individual criterion assesses fundamentally different quality properties of a Doppler image such as the anatomic plane of acquisition or the angle of Doppler application or the features of waveform Doppler optimization. As a result, our score distributions are less skewed and the median score is 4.

Among other strengths of this study are that the sample was randomly drawn from an unselected pregnant population undergoing routine examinations at 36 weeks, that is, the gestation where MCA—as part of the CPR—is most useful in assessing placental insufficiency. The sonographers who performed the measurements were appropriately trained sonographers or fellows performing ultrasound examinations within the standards of a tertiary UK NHS service and they were using regularly upgraded scan machines. The study was adequately powered and the use of PABAK is the recommended methodology for assessing image scoring agreement [8].

We also acknowledge some limitations. There was a statistically significant difference of mean score between the two reviewers but the magnitude of this difference was clinically insignificant and did not affect the overall reliability. The scoring cut-off used to define good and poor quality—though consistent with previous image scoring literature—is rather arbitrary. Given the low interdependence between criteria it could be argued that each criterion is absolutely essential for the image to be deemed satisfactory and that the quality threshold should be set higher than 4. However this does not invalidate the conclusions of this exercise which demonstrates that the scoring method is reliable. It is up to institutions to define the level of threshold in their clinical practice. Another limitation is that these MCA images were taken as part of a universal screening program for fetal growth and CPR but they were not performed specifically for peak systolic velocity measurement. Nevertheless the same quality principles underlie the latter measurement and it is reasonable to assume that the proposed scoring method is valid when MCA is used as a screening tool for fetal anemia. This scoring method cannot assess the effect of pressure applied on the ultrasound probe which is known to alter MCA values [17]. Image analysis is time-consuming and should not be the sole measure of quality control. However, it is a useful tool as part of a quality control strategy which may also include quantitative analysis of measurement distributions of individual sonographers, similar to those strategies employed for quality assurance of NT programs [9].

We propose that this objective scoring system is used to assess MCA Doppler measurement quality. Providers should use this regularly to audit the performance of individual sonographers in their institutions; and should decide locally the satisfactory score threshold in order to determine the need for feedback and retraining.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Reference ranges for Doppler indices of umbilical and fetal middle cerebral arteries and cerebroplacental ratio: systematic review

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KEYWORDS: cerebroplacental ratio; Doppler reference ranges; fetal growth restriction; methodology; middle cerebral artery Doppler; small-for-gestational age; umbilical artery Doppler

ABSTRACT

Objective *To assess studies reporting reference ranges for umbilical artery (UA) and fetal middle cerebral artery (MCA) Doppler indices and cerebroplacental ratio (CPR), using a set of predefined methodological quality criteria for study design, statistical analysis and reporting methods.*

Methods *This was a systematic review of observational studies in which the primary aim was to create reference ranges for UA and MCA Doppler indices and CPR in fetuses of singleton gestations. A search for relevant articles was performed in MEDLINE, EMBASE, CINAHL, Web of Science (from inception to 31 December 2016) and references of the retrieved articles. Two authors independently selected studies, assessed the risk of bias and extracted the data. Studies were scored against a predefined set of independently agreed methodological criteria and an overall quality score was assigned to each study. Linear multiple regression analysis assessing the association between quality scores and study characteristics was performed.*

Results *Thirty-eight studies met the inclusion criteria. The highest potential for bias was noted in the following fields: 'ultrasound quality control measures', in which only two studies demonstrated a comprehensive quality-control strategy; 'number of measurements taken for each Doppler variable', which was apparent in only three studies; 'sonographer experience', in which no study on CPR reported clearly the experience or training of the sonographers, while only three studies on UA Doppler and four on MCA Doppler did; and 'blinding of measurements', in which only one study, on UA Doppler, reported that sonographers were blinded to the measurement recorded during the examination. Sample size estimations were present in only seven studies. No predictors of quality were found on multiple regression analysis. Reference ranges varied significantly with important clinical implications for what is considered normal or abnormal, even when restricting the analysis to the highest scoring studies.*

Conclusions *There is considerable methodological heterogeneity in studies reporting reference ranges for UA and MCA Doppler indices and CPR, and the resulting references have important implications for clinical practice. There is a need for the standardization of methodologies for Doppler velocimetry and for the development of reference standards, which can be correctly interpreted and applied in clinical practice. We propose a set of recommendations for this purpose. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Doppler velocimetry is used to assess small-for-gestational-age (SGA) fetuses at risk of adverse perinatal outcome[1]. Doppler abnormalities in the umbilical artery (UA) are related closely to placental disease[2].

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On the other hand, changes in the fetal middle cerebral artery (MCA) reflect fetal cardiovascular adaptations to hypoxia or blood flow redistribution[3–5]. Thus, decreased pulsatility index (PI) has been considered a compensatory phenomenon to protect the fetal brain in the context of intrauterine growth restriction (IUGR)[6–9]. More recent work has suggested that the ratio of MCA-PI to UA-PI, the cerebroplacental ratio (CPR), is an independent predictor of fetal compromise[10], Cesarean section[11,12] and adverse perinatal outcome[13–16]. Therefore, UA and MCA Doppler indices and CPR are currently used to modify the scheduling of antepartum surveillance and, in some cases, to time delivery of the compromised fetus[2,10].

Whilst the methodology for acquiring fetal Doppler signals has been standardized[17], multiple reference ranges have been reported. Patterns of Doppler progression have been characterized clearly[18–22]. Thus, it has been reported that qualitative changes in UA Doppler, such as the presence, absence or reversal of end-diastolic velocity, clearly indicates an increased risk of fetal demise[23–25]. However, the association between quantitative changes in UA and MCA Doppler, as measured using PI, and perinatal and long-term outcomes has not been clearly established[26–28]. Furthermore, the value of Doppler ultrasound in appropriate- or large-for-gestational-age fetuses, post-term pregnancy[29], pregnancy complicated by diabetes[30] and uncomplicated dichorionic twin pregnancy[31] remains uncertain[32]. We hypothesize that this lack of evidence may be at least partially explained by different Doppler references used to define normal or abnormal findings, as shown recently in a systematic review of reference values for estimated fetal biometry[33].

The aim of this study was therefore to evaluate reference ranges for UA and MCA Doppler indices and CPR and specifically, first, to assess the methodological quality of studies on which these are based, using a set of predefined quality criteria for study design, statistical analysis and reporting methods, and, second, to estimate the clinical impact of using different reference charts.

METHODS

This study was conducted and reported in accordance with the checklist proposed by the MOOSE group[34] and the PRISMA statement for reporting systematic reviews and meta-analyses[35].

Eligibility criteria, information sources and search strategy

A search strategy was formulated in collaboration with a professional information specialist (Appendix S1). Relevant studies were identified through a search of MEDLINE, EMBASE, CINAHL and the Web of Science databases, including studies reported from 1954 to December 2016. Reference lists of retrieved full-text articles were examined for additional relevant citations. The search was not restricted by study design or methodology, however, articles published in only English or Spanish were considered.

Study selection

Observational (cohort or cross-sectional) studies aimed to create reference ranges for UA and MCA Doppler indices and CPR were included. Studies were excluded if they were a case–control study, their primary aim was not to construct Doppler reference ranges or they were limited to pregnancies < 20 or > 40 weeks' gestation (Table S1). All potentially relevant studies were retrieved and reviewed independently by two authors (S.R.-M. and D.O.) to determine inclusion. Disagreements were resolved through consensus.

Methodological quality assessment

The methodological quality of the full-text versions of eligible studies was assessed independently by the same reviewers and a medical statistician (E.S.-U.). Disagreements were resolved by consensus or consultation with two other reviewers (A.T.P. and E.F.). Authors' institutions were contacted in order to obtain a copy of the published article when this was not available from library sources.

A list of methodological quality criteria (Table 1) was initially developed by one of the authors (A.C.-A.), modified for use in the setting of Doppler, and agreed by the team not involved in data abstraction. These quality criteria are based on available published research[25,36,37], and are divided into two domains: study design, and statistical and reporting methods. In total, 24 quality criteria were evaluated.

Data extraction and synthesis

Following the review of included studies, all study details were entered into a Microsoft Excel 2010 spreadsheet. Every study was assessed against each of the criteria within the checklist and was scored as either 0 or 1 if there was a high or low risk of bias, respectively. The overall quality score was defined as the sum of low risk of bias marks, with the range of possible scores being 0–24. In order to assess agreement between reviewers in defining high or low risk of bias, the intraclass correlation coefficient of the interobserver complete score was calculated; this suggested excellent agreement (0.815; 95% CI, 0.66–0.90).

Multiple regression analysis was performed to assess the association between quality score and study characteristics that were not part of the scoring algorithm: year of publication; sample size of participating women; sample size of included ultrasound examinations; study duration; type of participating hospitals (teaching *vs* non-teaching); number of participating centers (single *vs* multicenter) and number of sonographers (single *vs* multiple). Statistical analyses were performed using Microsoft Excel 2010 and IBM SPSS Statistics version 20 (IBM, Armonk, NY, USA).

Table 1 Methodological quality criteria for study design and for reporting and statistical methods in studies presenting reference ranges for fetal Doppler parameters

Domain	*Low risk of bias*	*High risk of bias*
1. *Study design*		
1.01 Design	Clearly described as either cross-sectional or longitudinal	Not reported Mixture of cross-sectional and longitudinal data
1.02 Population	Women reported as coming from population of low risk of pregnancy complications	Women from unselected population; or selected; or at high risk of pregnancy complications; or not reported
1.03 Prospective data collection	Prospective study and ultrasound data collected specifically for purpose of constructing charts of fetal Doppler	Retrospective study, data not collected specifically for purpose of constructing charts of fetal Doppler, or unclear (e.g. use of routinely collected data)
1.04 Specific scan	Specific scan for research purposes	Routine scan in context of pregnancy assessment
1.05 Sample size	*A-priori* determination or calculation of sample size and justification	Lack of *a-priori* sample size determination or calculation and justification
1.06 Recruitment period	Reported	Not reported
1.07 Consecutive enrolment	Consecutively included patients	Did not include patients consecutively
1.08 Inclusion/exclusion criteria	Made clear that women at high risk of pregnancy complications were not included and that women with abnormal outcome were excluded, i.e. an effort was made to include as normal an outcome as possible As a minimum, the study population should exclude: multiple pregnancy; fetuses with congenital, structural or chromosomal anomaly; fetal death/stillbirth; women with disorders that may affect fetal growth or Doppler (at least should specify exclusion of women with pre-existing hypertension, diabetes mellitus, renal disease and smokers); pregnancy complications (at least pre-eclampsia, SGA/IUGR, prematurity, diabetes mellitus); delivery prior to 37 weeks	Study population included both low- and high-risk pregnancies, or women with abnormal outcome were not excluded Study population did not exclude fetuses or pregnancies with the characteristics described in the 'low risk' column Exclusions which would have a direct effect on the Doppler, such as fetuses found at birth to be small for dates
1.09 Method of dating pregnancy	Clearly described known LMP and sonogram before 14 weeks' gestation demonstrating crown–rump length that corroborates LMP dates (within how many days unspecified)	Not described clearly Gestational age assessment at >14 weeks or gestational age assessment not including ultrasonographic verification
1.10 Multicenter study	Study performed with more than one center collaborating	Performed at only one hospital
2. *Reporting and statistical methods*		
2.01 Perinatal outcome	Collected and reported prospectively	Not reported
2.02 Gestational age range	Reported	Not reported
2.03 Ultrasound machines and probe type used	Clearly specified	Not clearly specified
2.04 Reported sonographers	Number of sonographers reported	Not clearly specified
2.05 Sonographer experience	Experienced or specifically trained sonographers clearly reported	Not clearly specified
2.06 Blinded measurements	Sonographers were blinded	Not clearly specified
2.07 Ultrasound quality control measures	Should include the following: assessment of intraobserver variability; assessment of interobserver variability; image review; image scoring; image storage	Does not contain quality control measures
2.08 Protocol	Study described sufficient and unambiguous details of measurement techniques used for fetal Doppler parameters	Study did not describe sufficient and unambiguous details of measurement techniques used for fetal Doppler parameters
2.09 Number of measurements taken for each Doppler variable	At least three measures per fetus per scan	Single measure or not specified
2.10 Angle correction	Clearly specified	Not clearly specified

Continued over.

Table 1 *Continued*

Domain	*Low risk of bias*	*High risk of bias*
2.11 Statistical methods	Clearly described and identified	Not clearly described and identified
2.12 Report of mean and SD of each measurement and sample size for each week of gestation	Presented in a table or clearly described	Not presented in a table or not clearly described
2.13 Report of regression equations for mean (and SD if relevant) for each measurement	Reported	Not reported
2.14 Scatter diagram	Study included Doppler chart with mean and SD or centiles (at least 5th, 50th and 95th centiles)	Doppler charts not included

IUGR, intrauterine growth restriction; LMP, last menstrual period; SGA, small-for-gestational age.

RESULTS

The search yielded 2902 citations, of which 56 were considered for potential inclusion. The flowchart of the literature search is presented in Figure 1. Studies excluded from this review and the reasons for exclusion are listed in Table S1. A total of 38 studies from 22 countries met the inclusion criteria and were included in the final analysis[38–75]. The main characteristics, the overall study design and statistical and reporting methods quality scores for each included study are presented in Table S3.

The overall mean quality score for the included studies was 51.4% (95% CI, 47.1–55.8%), whereas quality scores for study design and statistical and reporting methods were 47.4% (95% CI, 42.6–52.1%) and 54.3% (95% CI, 48.8–59.7%), respectively. The earliest study was published in 1987[70] and the latest in 2016[39]. The median sample size of participating women was 206 (range, 13–2323; interquartile range (IQR), 70.75–675.25), whereas the median number of ultrasound examinations was 400 (range, 60–2323; IQR, 183.5–952). In total, UA and MCA Doppler reference ranges were reported in 30 and 19 studies, respectively; in 11 studies, reference ranges for both UA and MCA Doppler indices were reported, whereas only four studies reported reference ranges for CPR. PI was reported in 31 studies, resistance index in 22 studies and systolic-diastolic ratio in 21 studies. The overall methodology score was similar for the studies focused on UA (median 49.0%; range 20.8–70.8%), those focused on MCA (median 55.0%; range 29.1–79.1%) and those focused on CPR (median 54.1%; range 41.6–62.5%).

Data collection was prospective in 34 studies, but in only 19 studies was data collection explicitly for research purposes (Table S3). Thirteen studies had a longitudinal design, 23 were cross-sectional and one was mixed (cross-sectional and longitudinal); the design of the remaining study was not reported. Low-risk pregnancies were included in 22 (57.9%) studies. About half (53%) of the studies used a dating method considered to be at low risk of bias, namely either first-trimester measurement of crown–rump length (CRL) alone or the last menstrual period (LMP) confirmed by CRL. Overall, the demographic characteristics of the populations and any inclusion or exclusion criteria were not described in detail.

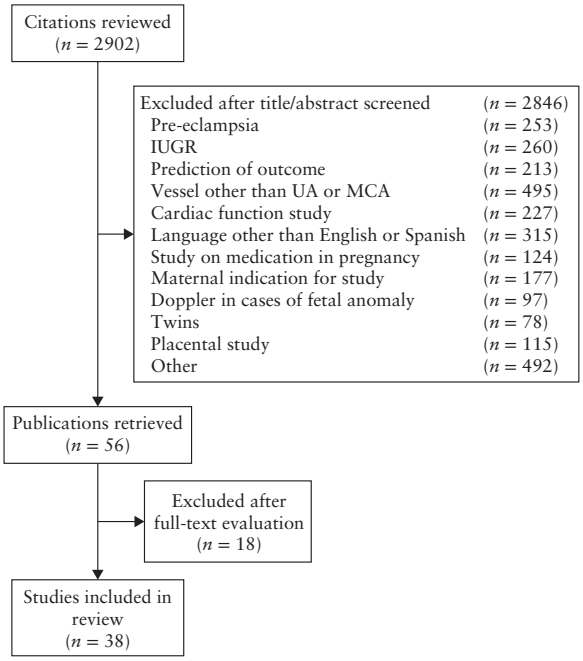

Figure 1 Flowchart summarizing inclusion of studies in systematic review. IUGR, intrauterine growth restriction.

The frequency of low risk of bias for each of the items in the two groups of methodological criteria (Table 1) for studies on UA and MCA Doppler indices and CPR are presented in Figures 2–4 and Table S2. The highest risk of bias was similar for studies on UA and MCA Doppler indices and CPR, and was noted in the following fields: 'multicenter study' (item 1.10), in which only three of the studies were performed in more than one center; 'ultrasound quality control measures' (item

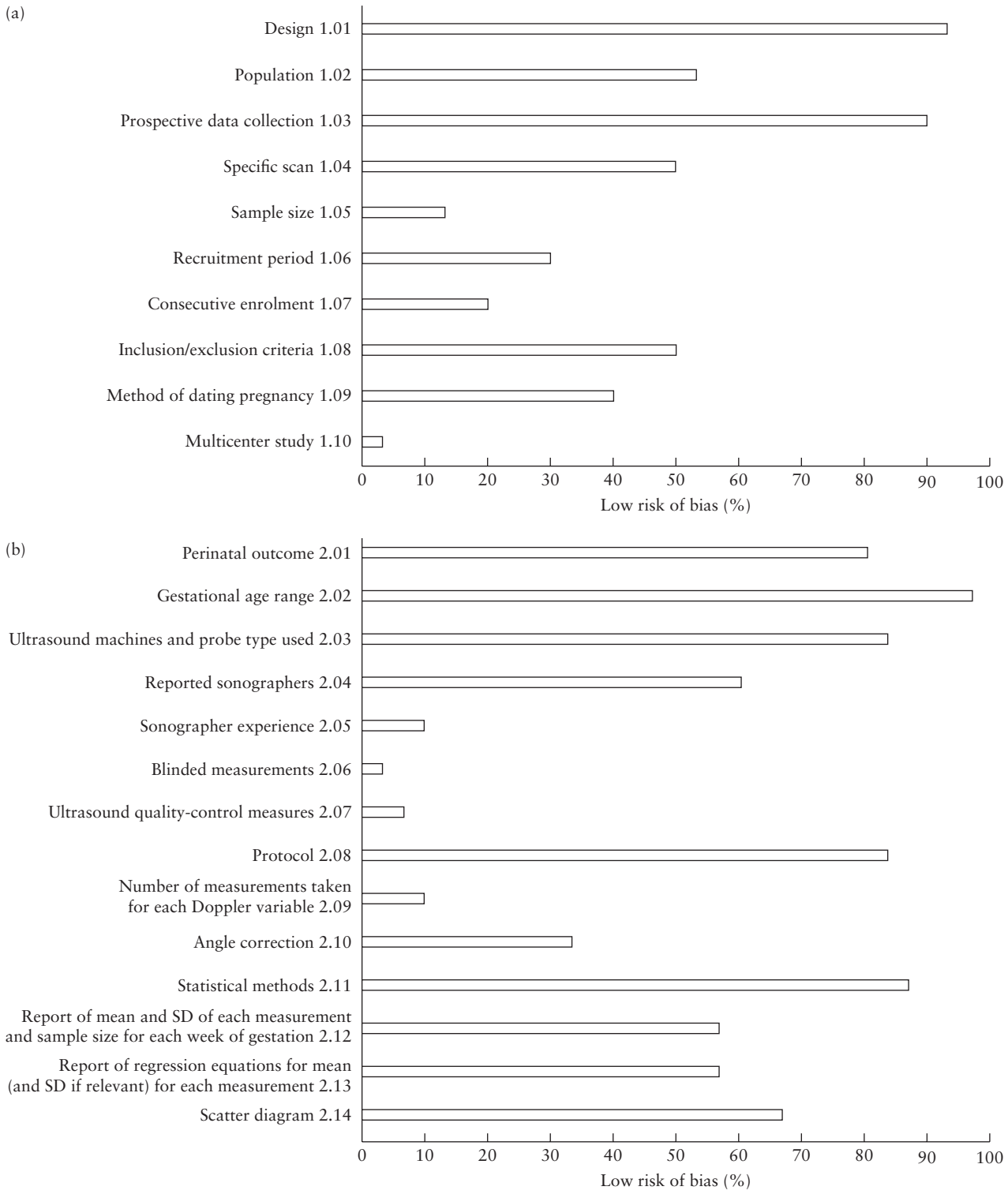

Figure 2 Methodological quality of 30 studies presenting umbilical artery Doppler reference ranges, according to study design (a) and reporting and statistical methods (b) criteria.

2.07), in which only two studies, focused on the UA, demonstrated a comprehensive quality-control strategy, and in which no study reported the use of an image scoring method for the purpose of ultrasound quality assurance; 'sonographer experience' (item 2.05), in which only three and four studies of UA and MCA Doppler, respectively, specified clearly the experience or training of the sonographers; 'blinded measurements' (item 2.06), in which sonographers in only one UA study were blinded to the measurement recorded during the examination and 'number of measurements' (item 2.09), which was apparent in only three studies. Furthermore, none of the CPR studies reported information on 'recruitment period' (item 1.06) (Figure 4).

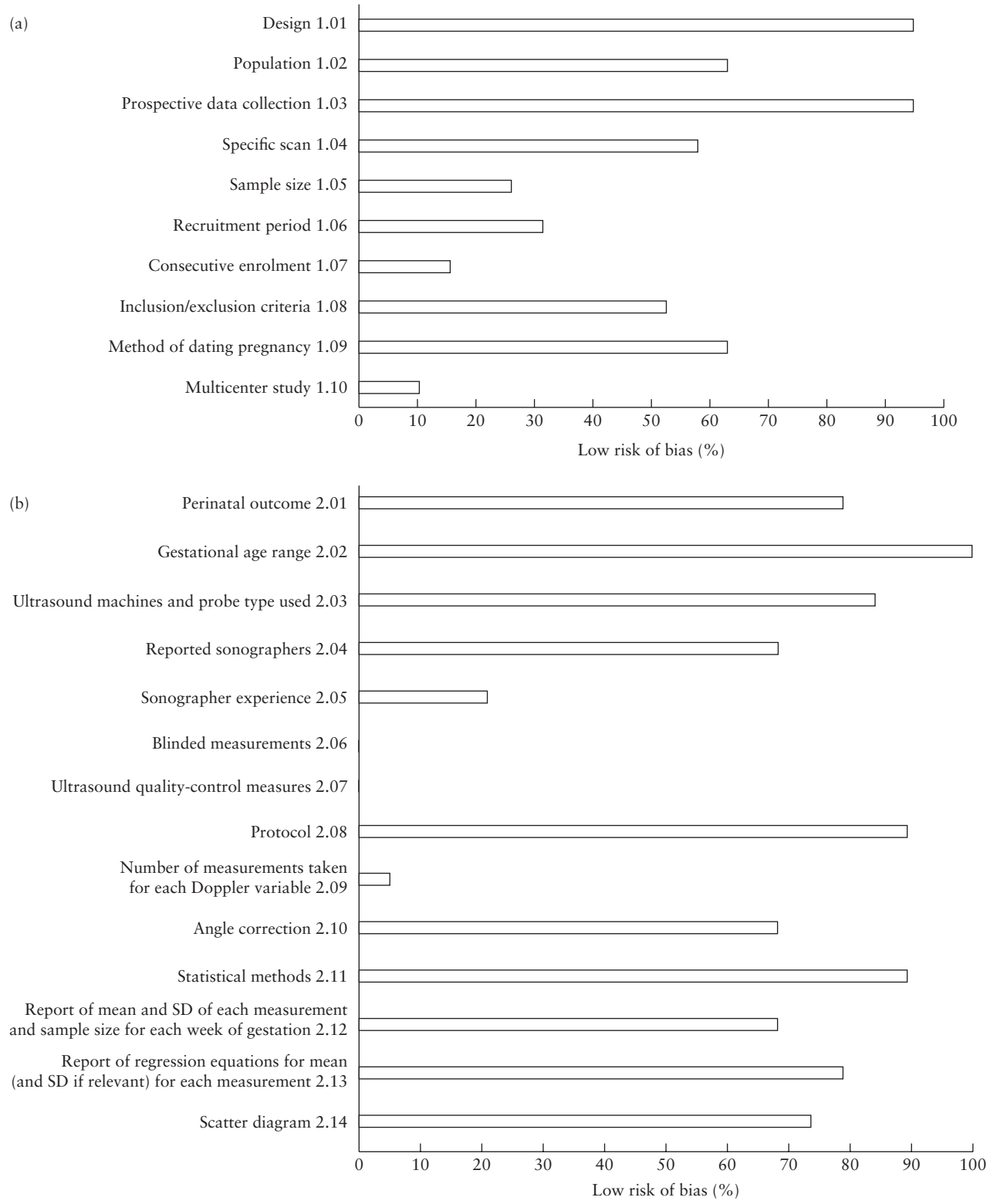

Figure 3 Methodological quality of 19 studies presenting fetal middle cerebral artery Doppler reference ranges, according to study design (a) and reporting and statistical methods (b) criteria.

Although some individual 'inclusion/exclusion criteria' of participants (item 1.08) were used in different studies, there was no study in which all of these criteria were used systematically (Figures 2–4). Similarly, 'sample size' calculation (item 1.05) was apparent in only seven studies (18.4%).

Results from individual studies were reported in the form of tables, equations or charts, as shown in Figures 2–4. Tables of mean and SD of each measurement and for each week of gestation were the most common method of presentation of results (24 studies).

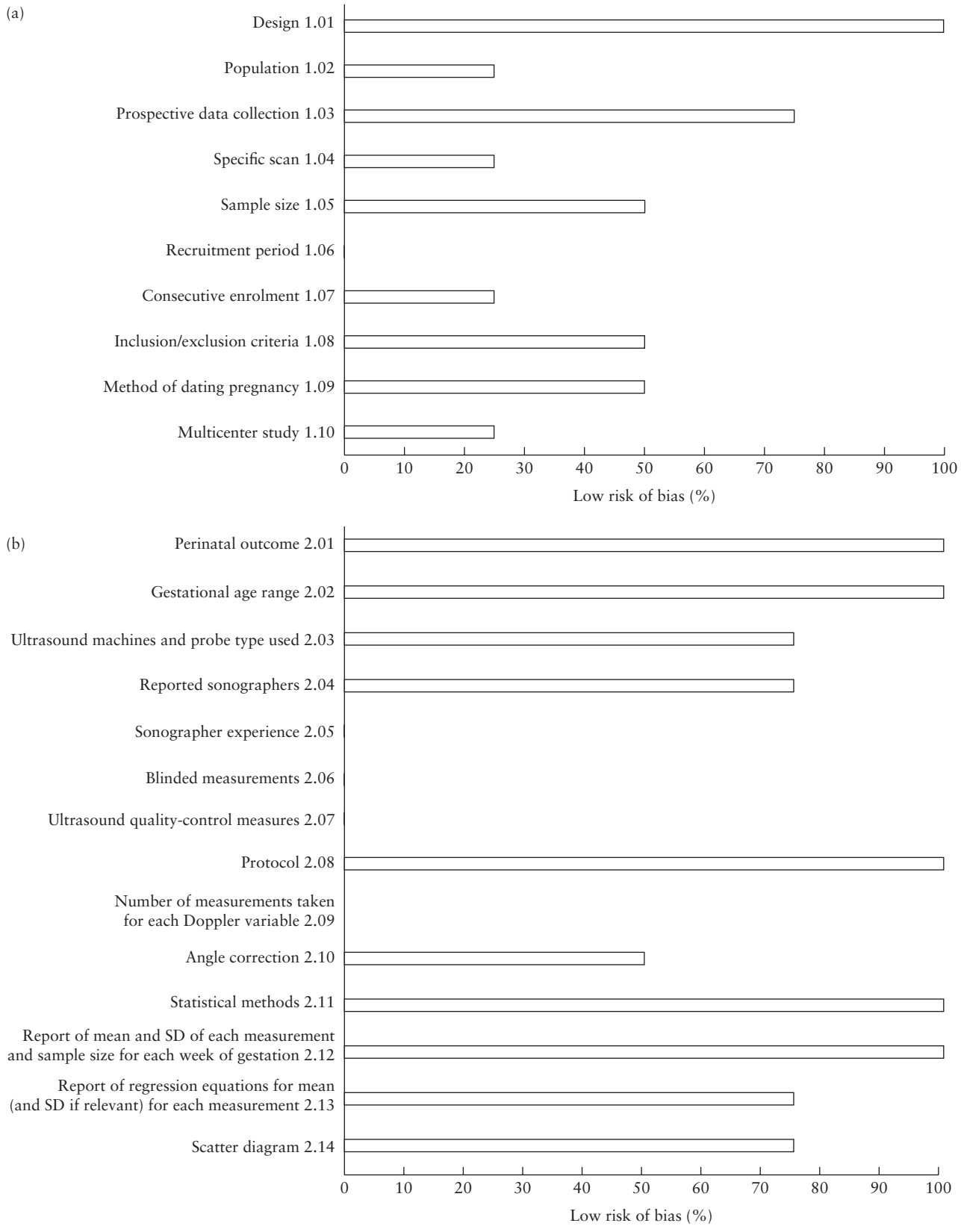

Figure 4 Methodological quality of four studies presenting cerebroplacental ratio reference ranges, according to study design (a) and reporting and statistical methods (b) criteria.

An equation for the mean and SD was reported in 23 of 38 studies, whereas printed charts of the median and centile curves were seen in 25 publications.

With regard to type of hospital, teaching hospitals ($n = 28$) did not have a significantly higher overall quality score when compared to non-teaching hospitals ($n = 10$;

Table 2 Values of 50th centile and clinically relevant cut-off for umbilical artery pulsatility index (UA-PI), middle cerebral artery pulsatility index (MCA-PI) and cerebroplacental ratio (CPR) in studies reporting reference ranges that had highest methodological quality scores

	UA-PI						*MCA-PI*						*CPR*					
	Medina Castro et al.[48]		*Parra-cordero* et al.[46]		*Arduini* et al.[71]		*Medina Castro* et al.[49]		*Seffah* et al.[38]		*Bahlmann* et al.[42]		*Morales-Roselló* et al.[40]		*Ebbing* et al.[47]		*Baschat* et al.[54]	
GA (weeks)	*50th centile*	*95th centile*	*50th centile*	*95th centile*	*50th centile*	*95th centile*	*50th centile*	*5th centile*	*50th centile*	*5th centile*	*Mean*	*5th centile*	*50th centile*	*5th centile*	*50th centile*	*5th centile*	*Mean*	*5th centile*
28	1.06	1.41	1.07	1.45	1.12	1.61	1.77	1.17	1.96	1.03	1.94	1.44	1.73	1.23	2.14	1.47	2.13	1.28
29	1.00	1.46	1.04	1.40	1.08	1.57	1.89	1.12	1.92	0.91	1.94	1.44	1.76	1.25	2.21	1.53	1.86	1.15
30	1.03	1.39	1.01	1.36	1.05	1.54	1.92	1.18	1.75	1.42	1.92	1.42	1.79	1.25	2.28	1.58	2.34	1.44
31	1.03	1.37	0.98	1.32	1.02	1.51	1.93	1.14	1.77	1.51	1.9	1.40	1.81	1.26	2.32	1.62	2.29	1.73
32	1.00	1.35	0.95	1.28	0.99	1.48	1.82	1.15	1.54	1.41	1.88	1.37	1.82	1.26	2.35	1.64	2.03	1.24
33	0.96	1.30	0.92	1.24	0.97	1.46	1.80	1.11	1.66	1.11	1.74	1.33	1.82	1.25	2.36	1.65	2.10	1.44
34	0.97	1.29	0.89	1.20	0.95	1.44	1.70	1.12	1.52	1.29	1.80	1.28	1.81	1.24	2.35	1.63	2.10	1.36
35	0.93	1.27	0.86	1.17	0.94	1.43	1.63	1.07	1.32	1.08	1.75	1.23	1.79	1.22	2.32	1.60	2.01	1.45
36	0.92	1.21	0.84	1.13	0.92	1.42	1.60	0.99	1.38	1.03	1.68	1.16	1.77	1.20	2.27	1.55	2.01	1.26
37	0.86	1.18	0.81	1.10	0.92	1.41	1.45	0.85	1.53	1.01	1.61	1.09	1.73	1.17	2.19	1.48	2.25	1.17
38	0.84	1.12	0.79	1.06	0.91	1.40	1.37	0.79	1.14	0.96	1.53	1.01	1.69	1.14	2.09	1.40	1.90	1.23
39	0.83	1.05	0.76	1.03	0.91	1.40	1.24	0.75	1.37	0.77	1.45	0.92	1.64	1.10	1.97	1.29	1.64	1.16
40	0.79	1.07	0.74	1.00	0.91	1.40	1.06	0.56	0.99	0.92	1.35	0.82	1.58	1.06	—	—	1.80	1.08

GA, gestational age.

52.2% *vs* 48.3%; $P = 0.4$). In line with these results, but contrary to a similar previous report[24], neither the year of publication ($P = 0.506$) nor the sample size of participating women ($P = 0.119$), ultrasound examinations ($P = 0.215$), study duration ($P = 0.251$), teaching hospital ($P = 0.395$), number of participating sites ($P = 0.278$) or number of sonographers ($P = 0.447$) were significant predictors of quality score on univariate or multiple regression analysis.

Differences in UA and MCA Doppler indices and CPR values between the studies that had the highest scores for quality showed that significant heterogeneity remained. For example, the 95th centile of UA-PI at 37 weeks of gestation was 1.41 in one chart[71], whereas it was 1.1 in another[46] (Table 2). Similar instances were also noted at various other gestational ages and in reference ranges for MCA-PI and CPR.

DISCUSSION

This study has shown that there is considerable heterogeneity in the methodological quality of ultrasound studies aimed at creating reference ranges for UA and MCA Doppler indices and CPR. These differences may at least partly explain the differences in reported reference ranges and these may in turn explain some of the discrepancies seen in perinatal research based on Doppler, including patterns of Doppler progression[19–21,76] or even long term outcome[15,26]. This review determined the potential risk of bias based on study design and statistical and reporting methods using a predefined quality-scoring sheet of 24 criteria to determine which of these studies were most likely to be relevant for clinical management.

The data were collected prospectively for research purposes in only half of the included studies. Using clinical information collected routinely to create a reference could be an important source of bias, with over-representation of at-risk cases. Sixteen studies were performed on unselected populations, including pregnancies with suspected IUGR. An unselected population ensures a better representation of the underlying population[77,78]. We consider that the aim of a fetal Doppler chart should be to depict how fetal hemodynamics should be under optimal conditions (a prescriptive standard) rather than how they often are (a descriptive reference)[79].

Three-quarters of the published references were performed by one sonographer. Multi-sonographer studies increase external validity and data consistency can be achieved by undertaking a formal standardization exercise prior to the start of a study[80]. A lack of blinding of researchers in studies has been shown to bias results[81] and the STROBE guideline recommends blinding in order to reduce such bias[82]. The effect of lack of blinding on expected-value bias has also been demonstrated in the field of prenatal ultrasound, although the magnitude of the effect is not well understood. It is suggested that such blinding should be undertaken not only in the research setting when creating ultrasound standards, but also in clinical practice in order to reduce such expected value

bias[83,84]; this occurred in only one study. Monitoring of ultrasound data quality through a comprehensive quality control strategy has been proposed as another way to ensure high quality and should ideally include the use of image scoring methods and the assessment of intra- and interobserver variability of measurement[85].

Accurate estimation of gestational age is a fundamental prerequisite for creating any fetal standard[36,86,87]. Only 20 studies used dating either by CRL alone or by LMP corroborated by CRL.

Approximately one-third of the studies did not report the results in the form of tables of fitted centile values, gestational age curve charts and regression equations for both the mean and SD[88]. Both the median and variance should be modelled as a function of gestational age in a manner that accounts for the increasing variability with gestation and provides smooth centile curves; goodness of fit testing should demonstrate that these curves describe accurately the structure of the raw data[45].

Even when assessing only those studies with the highest scores of methodological quality, clinical cut-offs varied significantly and could lead to important differences in clinical management (Table 2), demonstrating that about 40–50% of fetuses may be misclassified by using one chart rather than another.

The main strength of this review lies in the rigorous methodology used, which included: the implementation of guidelines for the conduct and reporting of systematic reviews of observational studies; the inclusion of a relatively large number of studies in the review and the use of a quality score checklist modified from that used in previous studies[13,36,37], which allowed an objective and quantitative assessment of study methodology. The use of a quality score in the form of a percentage allowed an objective rather than empirical assessment of quality, and also enabled regression analyses in order to identify predictors of quality or other trends.

A limitation of this study is the inclusion of studies published in only the English or Spanish language. It is possible that eligible studies published in other languages may have been missed. Furthermore, it may be possible that biological variation might account for differences in Doppler results. For example, Doppler parameters obtained at a very high altitude[89,90] may show some differences from measurements obtained near sea level due to adaptation; thus, reference ranges obtained at a very high altitude may not be appropriate to be considered normal ranges, in the same way as study sites at high altitude were excluded when creating fetal growth standards[91]. In addition, most Doppler territories, but in particular those of the MCA, show dynamic changes related to fetal movements, breathing or applied pressure from the ultrasound probe; however, while these changes can have an effect on an individual fetus, in studies creating ranges, these should not lead to bias unless standard guidelines were not followed. Another potential limitation was that the reviewers who performed the data abstraction were not blinded to the origin and authors of the included studies.

This systematic review has identified many ultrasound studies with poor methodology and reporting of reference ranges for UA and MCA Doppler indices and CPR. These should be taken into account in future studies and we recommend using a checklist of methodological good practices in further studies aimed at creating reference ranges for UA and MCA Doppler parameters and CPR; the criteria listed under low risk of bias (Table 1) would constitute the optimal methodological aspects for any future study. Our aim was to recommend reference ranges for use in clinical services based on the lowest risk of methodological bias (Table 2), however, even among these studies there are differences of clinical importance with what is considered normal and what is not; urgent research is needed to reach consensus on this issue or create charts of optimal quality for widespread use.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Search strategy

Table S1 Excluded studies and reasons for exclusion

Table S2 Evaluation of studies reporting reference ranges for fetal Doppler parameters according to methodological quality criteria

Table S3 Characteristics and methodological quality scores in studies presenting reference ranges for fetal Doppler parameters

Clinical impact of Doppler reference charts to manage fetal growth restriction: need for standardization

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Abstract

Objective: To assess clinical variability in the management of fetal growth restriction according to published Doppler reference values for the umbilical artery (UA), middle cerebral artery (MCA) and cerebroplacental ratio (CPR).

Methods: We performed a systematic search of MEDLINE, EMBASE, CINAHL, and the Web of Science databases between the years 1954 and 2018, and selected studies with the sole aim of creating fetal Doppler reference values for the UA, MCA and CPR. Variations between clinically relevant pulsatility index (PI) cut-off values were assessed. Simulation analysis was performed on a cohort of small-for-gestational-age (SGA) fetuses (n=617) to evaluate the impact of this variability on clinical management.

Results: The 10 most cited articles for each index (UA-PI, MCA-PI and CPR) from a total of 40 studies that met the inclusion criteria were analyzed. Wide discrepancies in reported Doppler reference values were found. MCA-PI showed the greatest variability in clinically relevant cut-off values (MCA-PI<5th) of up to 51% at term. However, the differences between the UA-PI (UA-PI>95th) and CPR (CPR <5th centile) cut-off values at each gestational age were from 20–40% and 15–35%, respectively. As expected by a simulation analysis, these differences showed great variability in the clinical management of SGA fetuses despite using the same protocol.

Conclusions: Selection of Doppler reference values can result in significant variability in the clinical management of intrauterine growth-restricted fetuses that may lead to suboptimal outcomes and inaccurate research conclusions. Therefore, an attempt to standardize fetal Doppler reference ranges is mandatory.

Introduction

Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity and mortality.[1] Apart from strict control during pregnancy and delivery, there are no other evidence-based treatments for suspected growth-restricted fetuses to ensure a healthy neonate that is not premature.[2,3] Currently, fetal ultrasound plays a critical role in the clinical management of IUGR.[4,5] The estimated fetal weight by ultrasound is the gold standard for the diagnosis of IUGR.[6] Nevertheless, Doppler measurement of foetal cardiovascular function is the basis for the schedule of controlled intervals and the optimum time to delivery.[7]

The methodology for the fetal Doppler evaluation is currently standardized.[8] Despite some controversy,[9] hemodynamic patterns of progression for early[10,11,12] and late[13] IUGR fetuses are well described. Qualitative changes in umbilical artery (UA) Doppler, such as absent or reverse diastolic flow, clearly indicate increased risk of fetal demise,[2,3,4,5] But the association between the sparing of the fetal brain, using UA, middle cerebral artery (MCA) pulsatility index (PI) Doppler, and cerebroplacental ration (CPR), and the perinatal and long-term outcomes has not been well determined.[14,15,16,17] Given the large number of published Doppler references, it could be hypothesised that this lack of evidence may be partially explained by the heterogeneity of this widespread use of different Doppler standards.

In a recent systematic review[18] we have shown that there is considerable methodological heterogeneity in studies reporting reference ranges for UA and MCA and CPR Doppler indices. The likely reason for these differences is due to methodological issues: thus, in the thirty-eight studies included, there was significant

potential for bias – for example, only two studies reported on ultrasound quality control measures; there was unclear reporting of the experience and training of the sonographers; and lack of blinding of measurements in all but one study.

It was evident from that review that differences between reference charts would have important implications for clinical practice. In this study we wanted to quantify the effect of these differences in a clinical setting. In order to do this we aim to analyze the potential heterogeneity of the most frequently used published Doppler reference charts of the UA-PI, MCA-PI, and CPR and assess the influence of the variability on the clinical management of small-for-gestational-age (SGA) fetuses.

Methods

A systematic review was performed to identify studies that aimed to establish normal values for the UA-PI, MCA-PI and CPR. The search strategy was designed by a professional information specialist and included studies reported from 1954 through December 2018 in MEDLINE, EMBASE, CINAHL, and the Web of Science databases (Table S1). The search was not restricted by study design or methodology, but only articles published in English or Spanish solely aiming to establish normal values between 20 and 40 weeks of gestation were considered. The number of citations for each study was obtained from the Web of Knowledge.[19] This study was conducted and reported in accordance with the checklist proposed by the MOOSE group.[20]

Studies were retrieved and reviewed independently by two authors (SR and DO) to determine study inclusion. Disagreements were resolved through consensus with a third reviewer (ATP). We selected the 10 most cited studies for each vessel to compare the most used published Doppler reference standards. An UA-PI over the 95th percentile and MCA-PI and CPR below the 5th percentile were considered to be clinically relevant cut-off values.[4,5,7] Clinical cut-off percentiles were calculated by the mean and standard deviation for gestational age when not reported by the authors.[21,22] Variability was expressed as a percentage and was obtained by subtracting the lowest PI value from the highest and dividing by the highest PI value for every week of gestation.

Finally, simulation analysis was performed on a cohort of 617 consecutive fetuses with an estimated fetal weight (EFW) below the 10th percentile[23], assessed in our centre from 24–41 weeks of gestation. IUGR was defined as an EFW below the 10th percentile

accompanied with whichever abnormal Doppler (UA-PI>95th, MCA-PI<5th, or CPR<5th); in which labour induction was recommended at 37 weeks of gestation.[4,5,7]

To assess the influence of the Doppler reference standard variability in the clinical management of SGA fetuses, every case was hypothetically classified and theoretically managed according to the same previously described protocol, using the highest and lowest cut-off values for the UA-PI, MCA-PI, and CPR for every gestational age.

Statistical analyses were performed using Microsoft Excel 2010 and IBM SPSS Statistics version 20.

Results

The database searches yielded 6243 possible citations for our systematic review. Figure 1 shows the entire process of analysis and selection of the studies. Forty published papers met the selection criteria, with their sole objective being to determine reference Doppler values. In accordance with our objective to determine the clinical impact of variability, we selected the Doppler reference values most used in clinical practice and research. Thus, we included the top 10 most cited Doppler reference values for MCA-PI and CPR. We included 13 UA-PI Doppler reference values instead of 10 to avoid selection bias, because four articles focused on UA presented the same number of citations. We only found five articles showing reference ranges of CPR. Table 1 describes the main characteristics and number of citations of the 19 selected studies.

The distribution of UA-PIs within the 95th percentile across all pregnancies for each study is plotted in Figure 2. Similarly, MCA-PIs and CPR within the 5th percentiles were plotted and are shown in Figures 3 and 4. Notably, great variability existed between the reference values for the different UA-PI, MCA-PI and CPR cut-offs, with clinical implications. Furthermore, many of the most cited references in the literature showed an anomalous distribution of their PI cut-off values during gestation, possibly due to inappropriate statistical analyzes[18].

Differences between the highest and lowest published values for each week of gestation for the UA-PI within the 95th percentile and MCA-PI and CPR within the 5th percentiles are expressed as percentages and are shown in Figure 5. The mean between the difference of the highest and lowest UA-PI within the 95th percentile for

each complete gestational age was 28.02% (range: 21–41%). These differences were much more marked in the case of the highest and lowest cut-off values for each gestational week for the MCA-PI within the 5th percentile, with a mean difference of 36.86% (range: 26.8–51.3%). These differences increased after 35 weeks of gestation, where the presence of an abnormal MCA-PI involves important modifications for clinical management. Finally, CPR presented the lowest variability, with a mean difference of 24.09% (range: 15–32.6%). Again, as expected, the highest variability for CPR was at term.

To evaluate the potential impact of this variability among Doppler PI cut-offs on clinical management, simulation analysis of a historical cohort of 617 consecutive SGA fetuses was performed (Table 2). Depending on the choice of the lowest or highest UA-PI greater than the 95th percentile and MCA-PI and CPR less than the 5th percentiles for each gestational age, the proportions of SGA fetuses classified as abnormal according to UA-PI, MCA-PI, and CPR varied from 24.5–2.1%, 0.9–23.1%, and 5.5–33.1%, respectively. According to several clinical guidelines,[4,5] induction of labour may be required for UA-PI>95th percentile, MCA-PI<5th, or CPR<5th percentiles at full term. Even following the same clinical protocol, the potential number of labour inductions for SGA fetuses at term could vary from 33.7–2.1%, 1.1–13.3%, and 5.6–23.3% depending on the PI cut-off variability of the UA, MCA, and CPR, respectively.

Discussion

This is the first systematic review to analyze the impact of variability among the most used Doppler reference charts on the clinical management of SGA fetuses.

In most cases, fetal growth restriction is thought to be a marker of uteroplacental insufficiency.[24] Angiogenic defects that result in placental pathology are collectively referred to as maternal vascular lesions of underperfusion.[25] Hence, UA-PI can indirectly reflect the dimensions of the villous vascular tree, blood flow resistance in the fetal compartment of the placenta, and relative risk of nutritional and metabolic deficiency[26,27]. Besides, a growing body of evidence suggests that MCA Doppler, alone or in combination with the UA-PI (i.e., CPR), may be helpful in identifying fetuses at risk of IUGR[28,29,30] as a surrogate marker of the redistribution of blood flow for vital organ prioritization[15]. UA-PI, MCA-PI and CPR are now the most widely used tool for control and decision making for SGA fetuses[4,5]. UA-PI vasoconstriction is defined according to a statistical cut-off of the 95th percentile[31]. Similarly, the 5th percentile defines brain vasodilation for the MCA-PI or CPR[31]. Therefore, appropriate Doppler reference values are needed to accurately estimate these cut-off points. Unfortunately, a systematic review recently published by our group revealed considerable methodological heterogeneity in studies reporting reference ranges for UA-PI, MCA-PI and CPR[18]. In this study, we showed large differences among fetal Doppler reference charts at clinically relevant cut-off values.

For our analysis, we rationed the most cited studies in the literature to be the most used for clinical practice and research purposes. The application of an appropriate methodology in these studies to fit the criteria for our study has been previously

described [18,32]. However, all the works included in this analysis present a high risk of bias in their design and methodology and no good correlation exists between the methodological quality and number of citations in the literature[18]. For example, the top three most cited studies by Arduni[34], Baschat[35], and Acharya[36] showed an important risk of bias due to the fact that they were only the sixth, eleventh, and ninth ranked studies based on methodological quality according to a recently published systematic review[18]. It could be argued that older works are more likely to be cited than more recent studies with higher quality methodology[33] because newer works have not had sufficient time to implant themselves in clinical practice.

We found important sources of bias in the most widely used studies.[18] Ultrasounds were not performed for research purposes,[34,35,38,40,43,44,50] neither the recruitment period,[34,35,37,38,39,41,42,44,48] or perinatal results were described,[34] and the study was performed at a single centre.[34,35,36,37,38,39,40,41,47,49] We also found a lack of reporting necessary sample sizes,[34,36,38,39,40,41,44,45,46,48,50] the gestational dating method,[35,36,37,38,41,50] experience of the sonographers,[34,36,37,38,41,43,44,49,50] and even the inclusion and exclusion criteria[36,38,39,41,44,49] and quality controls.[34,35,36,37,38,39,40,41,43,44,45,46,47,48,49,50] As shown in Figures 2, 3, and 4, an irregular distribution was observed among the cut-off values at gestational time points in many of the analyzed reference ranges, suggesting inappropriate statistical treatment of the data.

Identification of fetal risk of adverse outcomes is a challenge in perinatal medicine. The main objective for strict control of IUGR fetuses is to deliver a healthy newborn without extreme prematurity, but also in avoidance of intrauterine death and maternal or neonatal morbidity. We want to highlight the impact of the heterogeneity of the Doppler

reference values being used within clinical practice and research. Simulation analysis performed in a real cohort of SGA fetuses clearly showed that the use of inaccurate tools can lead to inaccurate decision making for important clinical issues. The optimal time for pregnancy completion for SGA fetuses is one of the main focuses of interest in IUGR research.[53,54,55] , according to our results, even with the use of a standardized clinical protocol, the Doppler reference values used have a significant clinical impact. For example, a rate of induction at term could range from 2.1–33.7% for UA-PI, 1.1–13.3% for MCA-PI, and 5.6–22.3% in the case of CPR. Notably, the broadest variation among the Doppler reference values is at full term, which is a critical moment to programme different therapeutic actions. From our point of view, this potential variability in the clinical management of SGA fetuses is unacceptable.

The main strength of this study lies in the rigorous methodology used; we performed a comprehensive systematic review including a relatively large number of studies. A limitation of this study is that the evaluation of the impact of Doppler reference value charts in clinical management was performed in a retrospective cohort of SGA fetuses controlled with specific Doppler references. Thus, our results could be potentially biased. Due to the high number of published Doppler value reference charts, it is unlikely that a prospective study with a similar aim was conducted. Another potential limitation of this study is the inclusion of studies published only in the English or Spanish language. Nevertheless, this restriction is unlikely to be a significant limitation because the top-cited Doppler reference value charts were always published in English, as expected. Additionally, the literature search did not have restrictions for year of publication because some of the older ultrasound Doppler studies are still used

in current clinical practice. Apart from the PI, other parameters such as systolic/diastolic ratio (S/D) are sometimes used for the management SGA fetuses. We did not include this analysis for two reasons: firstly, only three of the most cited published Doppler references (Ayoola[50], Acharya[36] and Fogarty[42]) give reference ranges for the umbilical artery S/D ratio, and one (Tarzamni[43]) mention the middle cerebral artery S/D ratio. Secondly, as we did not have data on the S/D ratio from the cohort of SGA fetuses that we used to perform the simulation analysis, this could not be included here. Although this is a potential limitation the relationship between PI, RI, S/D ratios mean that the principle, of reaching different clinical decisions depending on the reference chart used, still applies.

The selection of the Doppler reference values determines the significant variability in the clinical management of IUGR fetuses that may lead to suboptimal outcomes and inaccurate research conclusions. In conclusion, an attempt to standardize fetal Doppler reference ranges is mandatory.

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Figure legends

Figure 1. Study selection process.

Figure 2. UA-PI above the 95th percentile of the most cited reference standards throughout the pregnancy.

Figure 3. MCA-PI below the 5th percentile of the most cited reference standards throughout the pregnancy.

Figure 4. CPR below the 5th percentile of the most cited reference standards throughout the pregnancy.

Figure 5. Differences between the highest and lowest UA-PI>95th percentile, MCA-PI<5th,and CPR<5th percentiles for each gestational age.

Table 1. Main characteristics of the included studies

Reference	Year	Patients (n)	Scans (n)	Weeks	Study Design	No. of Citations (n)	Doppler

Arduini et al[52]	1990	1556	1556	20-42	Cross-sectional	325	UA/MCA
Baschat et al[52]	2003	306	306	20-40	Cross-sectional	199	UA/MCA/CPR
Acharya et al [52]	2004	130	513	19-41	Longitudinal	161	UA
Ebbing et al[52]	2007	161	566	21-39	Longitudinal	86	MCA/CPR
Wladimiroff et al[52]	1988	284	284	26-38	Cross-sectional	43	UA
Bahlman et al[52]	2002	926	926	18-42	Cross-sectional	59	MCA
Parra-Cordero et al[52]	2007	172	172	23-40	Cross-sectional	37	UA/MCA
Manabe et al[52]	1995	20	195	15-40	Longitudinal	16	UA
Fogarty et al[52]	1990	85	783	16-42	Longitudinal	13	UA
Tarzamni et al[52]	2009	1037	1037	20-40	Cross-sectional	9	MCA
Morales-Rosello et al[52]	2015	2323	2323	19-41	Cross-sectional	5	MCA/CPR
Medina Castro et al[52]	2006	2081	2081	20-40	Cross-sectional	5	UA
Medina Castro et al[52]	2006	727	727	20-40	Cross-sectional	4	MCA
Komwilaisak et al[52]	2004	312	312	20-37	Cross-sectional	4	MCA
Bahlman et al[52]	2012	1926	1926	18-40	Cross-sectional	3	UA/MCA
Romero et al[52]	1999	60	337	30-40	Longitudinal	0	UA
Ayoola et al[52]	2016	400	400	15-39	Cross-sectional	0	UA
Srikumar et al[52]	2017	200	773	19-40	Longitudinal	0	UA/CPR
Ciobanu et al[52]	2018	72417	72417	20-41	Cross-sectional	0	UA/CPR

Table 2. Number of small-for-gestational-age (SGA) fetuses classified as abnormal for UA-PI, MCA-PI, and CPR by the maximum and minimum published cut-off values for each gestational age. (Simulation from a cohort of 617 consecutive SGA fetuses)

	Number of SGA fetuses with abnormal Doppler	
Umbilical Artery PI	**Lowest UAPI>95 (%)**	**Highest UAPI>95 (%)**
Total* SGA (n=617)	151 (24.5%)	13 (2.1%)
SGA>37 weeks (N=90)	32 (33.7%)	2 (2.1%)
Middle Cerebral Artery PI	**Lowest MCA<5 (%)**	**Highest MCA<5 (%)**
Total SGA* (n=585)	5 (0.9%)	135 (23.1%)
SGA>37 weeks (n=90)	1 (1.1%)	12 (13.3%)
Cerebroplacental Ratio	**Lowest CPR<5 (%)**	**Highest CPR<5 (%)**
Total SGA* (n=577)	32 (5.5%)	191 (33.1%)
SGA>37 weeks (n=90)	5 (5.6%)	21 (23.3%)

** SGA fetuses from 24 to 41 weeks.*

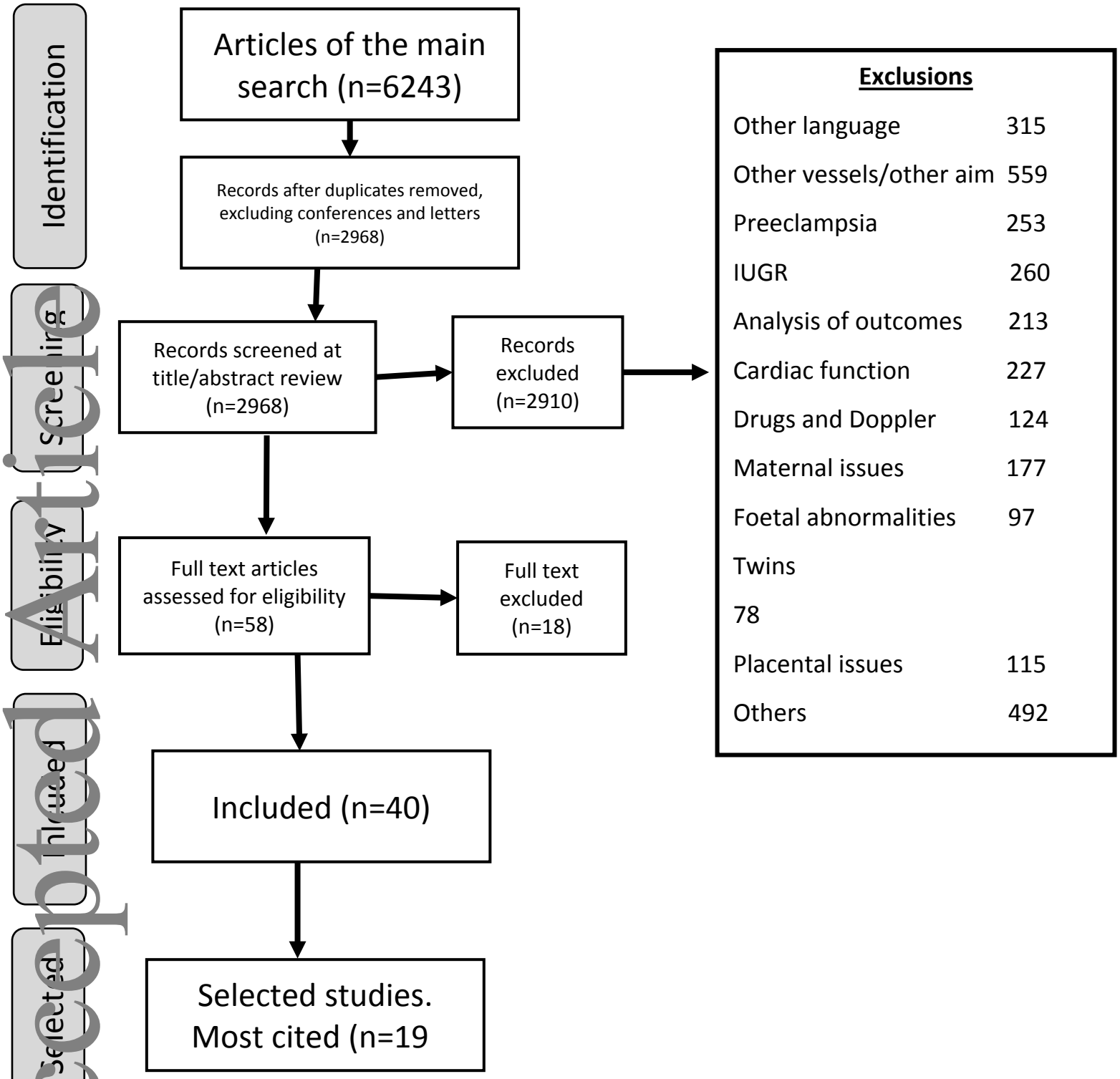


Figure 2. *Pulsatility index above the 95th percentile of the most cited umbilical artery reference standards throughout the pregnancy*.

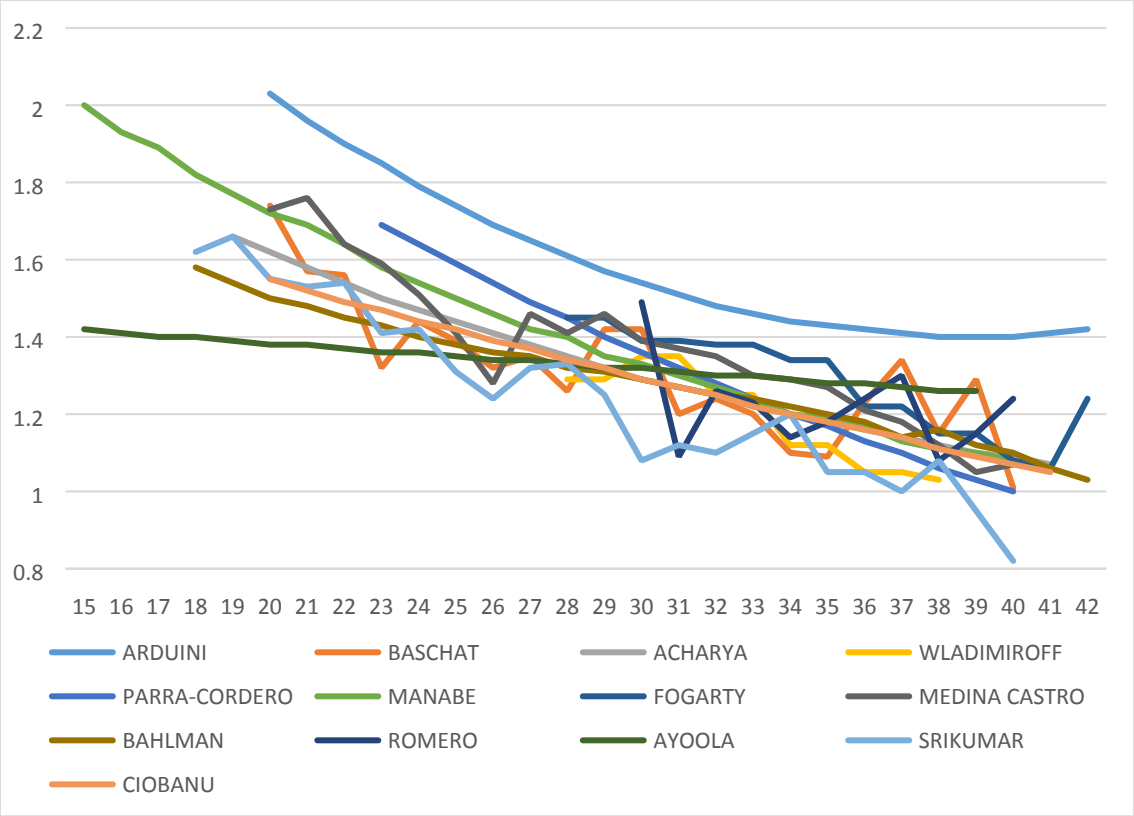


Figure 3. *Pulsatility index below the 5th percentile of the most cited middle cerebral artery reference standards throughout the pregnancy*.

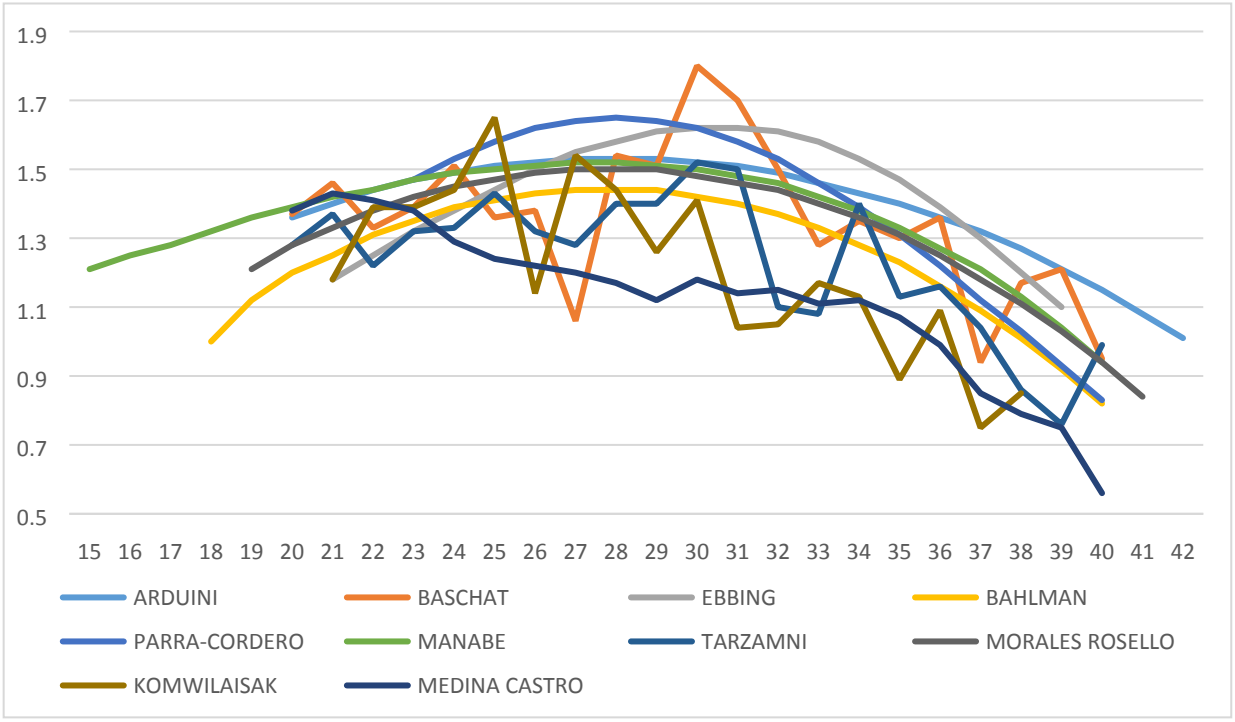


Figure 4. Pulsatility index below the 5th percentile of the most cited cerebroplacental ratio reference standards throughout the pregnancy.

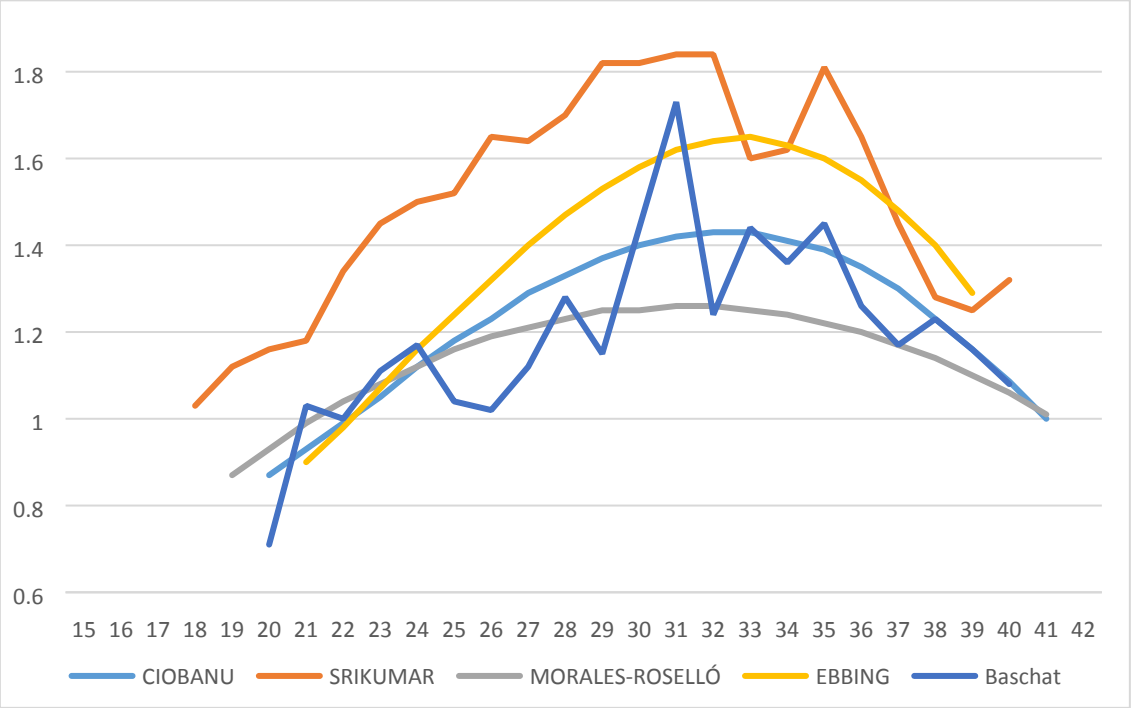
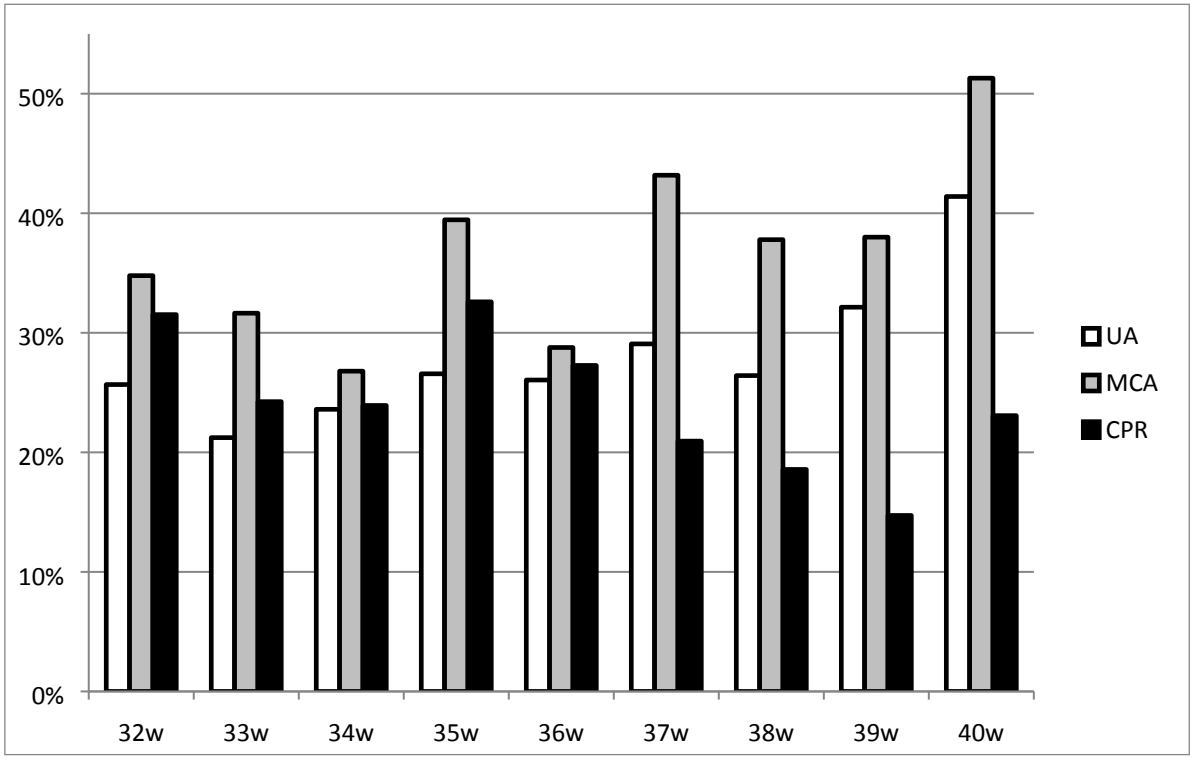


Figure 5. Differences between the highest and lowest pulsatility indices for UA>95th percentile, MCA<5th,and CPR<5th percentiles for each gestational age.



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Re: ISUOG Practice Guidelines on ultrasound assessment of fetal biometry and growth: time to pay attention to bias in Doppler studies

We congratulate ISUOG's Clinical Standards Committee on the recent publication of the Practice Guideline on ultrasound assessment of fetal biometry and growth[1]. They should be commended on what is an important piece of evidence gathering and interpretation. This work is linked intricately with the attempt to determine an international definition of fetal growth restriction (FGR)[2]. Given the fact that determining growth potential has not been possible yet, agreeing upon a clinically useful definition of FGR was an overdue first step to homogenized clinical practice; this work should also assist future research projects and the comparison of different studies on FGR.

The performance and interpretation of fetal biometry is the most important component in the diagnosis and monitoring of poor fetal growth. Reliable ultrasound charts are necessary for the prenatal assessment of FGR. Considerable methodological heterogeneity with high risk of bias in ultrasound studies aimed at creating charts of fetal size has been reported previously[3]. We therefore agree with the ISUOG Practice Guideline[1] which, for the first time, recommends both the use of prescriptive standards of growth as the best strategy to avoid methodological bias and comprehensive quality control.

It is time now to pay attention to the methodological quality of Doppler. Alongside fetal biometry, assessment of the placental and fetal circulation is the basis for the diagnosis and management of FGR. When abnormalities are severe, there is relatively clear evidence, such as absent or reversed frequencies in the umbilical artery (UA). However, in late or mild growth restriction, more subtle fetal hemodynamic progression is seen, such as elevated impedance to flow in the UAs, or brain sparing, detected by means of abnormal cerebroplacental ratio (CPR) or middle cerebral artery (MCA) Doppler. Although these findings are associated with adverse outcome[4], uncertainty remains around their clinical value in decision-making and the potential associated long-term consequences. This lack of evidence may be at least partially explained by the considerable methodological heterogeneity in studies reporting reference ranges for UA and MCA Doppler indices and CPR, as shown recently in a systematic review[5].

Methodological limitations in studies on which we base our clinical decisions have been evaluated poorly in the past. Inaccurate definitions and bias can lead to misinterpretation of clinical evidence, mistaken diagnosis and incorrect management of patients. In our view, the use of Doppler for clinical and research purposes in late or mild FGR should be accompanied by similar strategies to those applied previously in fetal biometry charts: by producing standards and reducing the risk of bias. Thus, there is urgent need for developing methodologically appropriate Doppler reference tables and including in practice guidelines concrete recommendations on the selection of the best Doppler reference standards.

Not all questions in nature have answers. It is possible that our lack of knowledge in certain fields is simply due to the fact that answers are not there, and we should accept this with modesty. However, we should not tolerate the ineffectiveness of clinical decision-making due to biases, methodological errors or absence of consensus on basic issues.

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International prescriptive fetal brain Doppler standards (FETHUS project): study protocol

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International prescriptive fetal brain Doppler standards (FETHUS project): study protocol

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KEYWORDS: Doppler, Doppler reference values, Doppler standards, Umbilical artery, Middle cerebral artery, Cerebroplacental ratio, intrauterine growth restriction.

ABSTRACT

Introduction: Existing literature does not provide conclusive evidence about benefits of fetal Doppler and its association with perinatal and long-term outcomes. The lack of evidence may be explained by different Doppler references used to define normal or abnormal findings. Considerable methodological heterogeneity and high risk of bias in studies reporting fetal Doppler reference ranges, has been recently reported. Thus, our aim is to develop methodologically robust and prescriptive umbilical artery (UA) , middle cerebral artery (MCA) Doppler and cerebroplacental ratio (CPR) standards for practical clinical applications as an international benchmark for the assessment of fetal brain Doppler.

Methods and analysis: This is a multicentre, international and population-based prospective longitudinal cohort study. The study will be carried out simultaneously, in eight centres from five different countries. Only healthy low-risk singleton pregnant women with adequate obstetric control, with an evolution of pregnancy without complications and in ideal healthy environment meet with inclusion criteria. After the routine second trimester US scan, an appointment for the research US scans will be programme every 5 weeks. Each patient will have a maximum of 4 scheduled visits, in addition to their routine gestational control. UA and MCA PI, RI and S/D, as well as cerebroplacental ratio (CPR) standards, will be constructed based on fractional polynomial regression. The maternal and fetal outcomes will be recorded and analysed after delivery. An initial recruitment of 1000 patients and 5000 Doppler ultrasound scans is required to achieve the proposed objectives.

Ethics and dissemination: The study will be conducted in accordance with the principles of Good Clinical Practice. This study was approved by the Clinical Research Ethics Committee (CEIC) of Aragon, on 24th July 2019. The trial is registered in the public registry ISRCTN according to Science Law 14/2011, and the results will be published in an open access journal.

Strengths and limitations of this study

- This is a multicentre, international and population-based prospective longitudinal study.
- The study protocol addressed most of the important limitations identified in previous studies.
- The sample size is larger than most previous studies.
- Follow-up of the offspring is limited to the neonatal period.

1. INTRODUCTION

Doppler ultrasound in obstetrics

The use of Doppler ultrasound to investigate the pattern of waveforms in the umbilical artery (UA) during pregnancy was first reported in 1977.1 Since then, ultrasound technology has developed further and much more complex assessment of fetal circulation has become standard clinical practice in obstetrics units worldwide. Doppler assessment of fetal well-being in high-risk pregnancies improves several clinical outcomes and reduces the risk of perinatal deaths and may result in fewer obstetric interventions.[2] However, existing literature does not provide conclusive evidence about its benefit as a screening tool in all pregnancies.[3]

Different Doppler modalities are used in obstetrics: continuous-wave, pulsed-wave, colour and power Doppler flow.[4] While colour and power Doppler provide visualisation of the blood flow and its direction, pulsed Doppler allows reproducible measurements of the blood velocities. The measurements obtained will reflect, in any vessel studied, the cardiac contraction force, density of the blood, vessel wall elasticity, but more importantly peripheral and downstream resistance.[5] Doppler abnormalities in the umbilical artery (UA) are related closely to placental insufficiency,[6] whilst changes in the fetal middle cerebral artery (MCA) reflect fetal cardiovascular adaptations to hypoxia or blood flow redistribution to protect the fetal brain. In extreme circumstances, qualitative changes in the blood flow of the UA such as the absence or reversal of end-diastolic velocity, clearly indicates an increased risk of fetal demise.[7,8]

Notwithstanding, in an attempt to quantify the Doppler signals accurately and reproducibly, flow of the umbilical and fetal arteries is most often expressed either by pulsatility index (PI) or resistant index (RI).[9] These indices reflect the downstream vascular resistance by quantifying the differences between the peak systolic and the end diastolic velocity within blood vessels of interest in each cardiac cycle.[10] Alongside fetal biometry, assessment of the placental and fetal circulation is the basis for the diagnosis and management of fetal growth restriction[11] and fetal anaemia.[12] However, the association between quantitative changes in UA and MCA Doppler with perinatal and long-term outcomes has not

been clearly established.[13,14] Furthermore, the value of Doppler ultrasound in appropriate-for-gestational-age fetuses[3], post-term pregnancy[15], uncomplicated dichorionic twin pregnancy pregnancy[16] and diabetes[17] remains uncertain.

Cerebroplacental ratio (CPR) is calculated by dividing the Doppler index (pulsatility index (PI), resistance index (RI), or systolic/diastolic ratio (S/D)) of the MCA by that of the UA. Physiologically, CPR represents the interaction of alterations in blood flow to the brain, as manifest by increased diastolic flow as a result of cerebrovascular dilatation due to hypoxia and increased placental resistance, leading to decreased diastolic flow in the UA.[18] The cerebroplacental ratio (CPR), has been shown to be more sensitive to hypoxia than its individual components in animal and clinical models[19,20], but the test's ability to predict adverse perinatal outcome in this entity has been questioned.[21]

Study justification

Reliable Doppler references ranges are necessary for the assessment fetal well-being. The lack of evidence may be at least partially explained by different Doppler references used to define normal or abnormal findings. Our group has recently reported a systematic review showing considerable methodological heterogeneity and high risk of bias based on study design and statistical and reporting methods in studies reporting reference ranges for UA and MCA Doppler indices and CPR, with important implications for clinical practice. [22] Selection of methodologically biased Doppler reference values can result in significant variability in the management of FRG, that may lead to misinterpretation of clinical evidence, mistaken diagnosis, incorrect management of patients and inaccurate research conclusions.[23] The goal of any Doppler-triggered management protocol is to improve perinatal mortality and morbidity. Early antenatal detection, treatment where appropriate, and timely delivery could minimise the risks significantly. But an unnecessary early intervention may result in excess morbidity from prematurity and considerable anxiety in families and clinicians, whilst a delay may result in a stillbirth or severely compromised newborn.[2]

Standardization of methodologies for Doppler velocimetry and developing methodologically appropriate Doppler reference ranges which can be correctly

interpreted and applied in clinical practice, are urgently needed. Thus, our aim is to develop methodologically robust Doppler reference standards according to a set of quality recommendations[22,45], for practical clinical applications as an international benchmark for the assessment of fetal brain Doppler.

Conceptual issues: prescriptive approach

We aimed to extend the same prescriptive approach with international representation promoted by World Health Organization[24,25] and the INTERGROWTH[26] investigators into fetal Doppler. References, traditionally regarded as descriptive, are used for comparing different populations, while standards are prescriptive, implying a value judgment of optimal development to be followed by individual pregnancies. There is considerable evidence to justify using such international standards in the field of perinatal medicine. To construct prescriptive fetal Doppler standards require the inclusion of low-risk singleton pregnancies living in environments with no socio-economic constraints on fetal development, and receiving up-to-date, evidence-based, medical care and appropriate nutrition. Only data collected specifically for that purpose should be used, in order to avoid clinical bias. Our project is, therefore, a prospective, population-based study using standardised methodology in geographical areas where there is high quality maternal and neonatal care. We believe these standards will be unique because we deliberately addressed in the study protocol most of the important limitations that were previously identified [22]

2. OBJECTIVES

2.1. Primary objective

To develop methodologically robust and prescriptive umbilical artery (UA), middle cerebral artery (MCA) Doppler and cerebroplacental ratio (CPR) standards for practical clinical applications as an international benchmark for the assessment of fetal brain Doppler.

2.2. Secondary objectives

a. To examine the effect of maternal and fetal physiological variables at the time of ultrasound, such as the maternal body mass index, fetal and neonatal weight, sex, placental weight and fetal heart rate, on the fetal brain Doppler indexes.

b. To develop and objective and standardized protocol to asses the image quality and the reliability of the middle cerebral artery (MCA) and the umbilical artery (UA) Doppler.

3. METHODS

3.1. Study design

This is a multicentre, international and prospective longitudinal cohort study. The study will be carried out simultaneously, in the Obstetrics Departments of the Hospital Clinico Universitario (Zaragoza, Spain), Hospital Universitario Virgen de la Arrixaca (Murcia,Spain), Hospital Universitario de Cruces (Bilbao, Spain), St. George's Hospital (London, United Kingdom), Hôpital Necker-enfants maladades (Paris, France), Hospital Universitario de Chile (Santiago, Chile), Casa di Cura Santa Famiglia (Rome, Italy) and Karolinska University Hospital. (Stockholm, Sweden).

3.2. Eligibility criteria

Study Participants

In accordance with the prescriptive and high methodological quality approach, inclusion criteria and definitions meet with those previously published by the INTERGROWTH-21st Project.[26]

Included centres should have an adequate clinical infrastructure in a healthy environment. (Table 1) Only healthy low-risk pregnant women with adequate obstetric control, with an evolution of pregnancy without complications and in ideal healthy environment meet with inclusion criteria. (Table 2)

Exclusion Criteria

The participant may not enter the study if any of the following apply:

1. Suspected congenital malformations, genetic syndromes and/or infections
2. Planned delivery in other institution.
3. Risk of developing severe fetal anaemia.

Discontinuation/Withdrawal of participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the principal investigators from each centre may discontinue a participant from the study at any time when considered in case of:

1. Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
2. Significant protocol deviation
3. Withdrawal of consent
4. Loss to follow up

3.3. Sample size estimation

Sample size is one of the most important factors determining the precision of normal reference ranges. The accuracy of estimated centiles is inherently variable; extreme centiles (e.g. 5th, and 95th centiles) exhibit large imprecision because there are, by definition, few observations at extremes of the distribution, while the median has the greatest precision. Thus, to estimate extreme centiles with great precision, a large total sample size is required.[27] According to the literature,[28,29] a longitudinal design has greater efficiency and power than a cross-sectional design for the estimation of references ranges through pregnancy. A longitudinal study allows estimating the variability of Doppler variables between fetuses, and more accurately portraying the hemodynamic pattern over time for the population. Therefore, to estimate the 5th and 95th centiles with the same precision, a longitudinal study would require approximately half to one-third the sample size of a cross-sectional study.[30]

In a longitudinal study, the effective sample size depends not only on the number of individuals in the study but also on the number of repeated measurements per individual, whether the measurements are taken in replicate, the method used for curve fitting and smoothing, and the timing of the measurements.[28,29] Following previous recommendations[31] for longitudinal ultrasound estimation of variables through gestation, a total of 4000 ultrasound scans are required to reach a maximum precision of 0.02 standard deviations for the 5th and 95th percentiles. An increase in the number of explorations it would increase the cost, time, and manpower without increasing the precision of the results. According to other similar previous studies[32], each patient will have a maximum of 5 Doppler ultrasounds scans, at the time of inclusion at 20 weeks and every 5 weeks until delivery. Therefore, we expect a rate of loss or withdrawal of around 20% of the patients initially recruited, so an initial recruitment of 125 patients is required in each of the 8 centers involved (a total of 1000 patients and 5000 Doppler ultrasound scans) to achieve the proposed objectives. The chosen sample size is larger than most previous studies.

3.4. Study protocol

a. Follow up schedule

Every pregnant meeting the inclusion criteria will be invited to participate in our study immediately after the routine second trimester US scan. If consents, an appointment for the research US scans will be programme every 5 weeks. All the included centres will initiate the recruitment simultaneously. Twelve to thirteen patients per week will be recruited during ten consecutive weeks. As the study requires enough and similar number of patients through every week of gestation from inclusion to delivery, study visits will be scheduled according to 5 weekly patterns (Table 3). Each patient will have a maximum of 4 scheduled visits, in addition to their routine gestational control. As described in figure 1, the collection of information will be carried out for 32 consecutive weeks or until all the pregnancies included finished in order to collect the variables related to the perinatal outcome.

b. Exploration protocol

All the exams will be carried out by skilled personal with experience in fetal medicine according to the standard methodology. In case of any anomaly would be, it will proceed immediately according to the usual clinical protocols. The detailed measurement protocols, including graphical displays of measurement techniques, and the unique standardization procedures for all measurements been reported elsewhere.[33]

We will collect information on maternal history and evolution of pregnancy at inclusion and follow up controls. At each visit, maternal weight, heart rate and blood pressure[34], as well as a basic ultrasound scan including fetal heart rate and amniotic fluid[35] fetal head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL) will be performed.[36] Umbilical artery (UA) and Middle cerebral artery (MCA) Pulsatility Index (PI), Resistance Index (IR) and Systole/Diastole (S/D) will be measured three times from three separately obtained ultrasound images. [37] Once the pregnancy finish, we will complete the perinatal result from the usual clinical records.

3.5. Outcomes and control variables

Main outcomes

1. Umbilical artery Doppler (AU); continuous. Pulsatility Index (PI), Resistance Index (IR), Systole/Diastole (S/D) [37]
2. Middle cerebral artery Doppler (MCA); continuous. Pulsatility Index (PI), Resistance Index (IR), Systole / Diastole (S / D). Maximum systolic velocity (S/D) [37]
3. Cerebroplacental ratio (CPR); continuous.[37]

Secondary outcomes

1. Fetal growth restriction[38]; Binary (Yes / No)
2. Preeclampsia[39]; Binary (Yes / No)
3. Severe preeclampsia[39];Binary (Yes / No)
4. Preterm delivery before 37 weeks of gestation; Binary (Yes / No)

5. Emergency caesarean section due to fetal distress; Binary (Yes / No)
6. Neonatal acidosis (arterial pH <7.10 + EB> 12mEq / L); Binary (Yes / No)
7. Perinatal mortality (> 22 weeks of gestation - <28 days postpartum); Binary (Yes / No)
8. Neonatal Intensive Care Unit admission; Continuous (days)
9. Significant neonatal morbidity (convulsions, intraventricular haemorrhage> grade III, periventricular leukomalacia, hypoxic-ischemic encephalopathy, abnormal electroencephalogram, necrotising enterocolitis, acute renal failure (serum creatinine> 1.5 mg / dL) or cardiac failure (requiring inotropic agents); Binary
10. Perinatal mortality; Binary (Yes / No)

Control variables

1. Maternal age at birth; Continuous (years)
2. Smoking during pregnancy; Continuous (cigarettes / day)
3. Maternal weight at the booking; Continuous (Kg)
4. Maternal height; Continuous (cm)
5. Maternal ethnic origin; categorical (Europe, Africa, South America, Maghreb, Asia, Other)
6. Parity (number of deliveries> 22 weeks); Discrete
7. Previous preeclampsia; Binary (Yes / No)[39]
8. Previous gestational hypertension; Binary (Yes / No)[39]
9. Previous growth restricted fetuses (neonatal weight <10th percentile)[40]; Binary (Yes / No)[38,40]
10. Diastolic blood pressure; Continuous (mmHg)[39]
11. Systolic blood pressure; Continuous (mmHg)[39]
12. Maternal heart rate; Continuous
13. Fetal heart rate; Continuous
14. Biparietal diameter; Continuous (mm) [32]
15. Head Circumference; Continuous (mm) [32]
16. Abdominal circumference; Continuous (mmHg)[32]
17. Femur length; Continuous (mmHg)[32]
18. Estimated fetal weight;[41] Continuous (mmHg)[42]
19. Deepest amniotic fluid pocket; Continuous (mm)[43]

20. Gestational age at inclusion; Continuous (days)
21. Last menstrual period (dated by ultrasound <14 weeks according to CRL[44]); Continuous (days)
22. Gestational age at birth; Continuous (days)
23. Neonatal weight; Continuous (g)
24. UA and MCA Doppler Angle correction; Continuous (grades)
25. Ultrasound machine and probe; used in the scan; discrete (names)

3.6. Quality control

We will carry out a strict quality control, following the recommendations previously published by our group [22]. Ultrasound machines will be equipped with real-time, grayscale, two-dimensional (2D) transducers, and have adjustable and displayed output power, freeze frame and zoom options as well as electronic calipers. Doppler ultrasound measurements will be recorded using a 2–5, 4–8 or 2–7-MHz transabdominal transducer. All the images will be storage, scored and reviewed following quality criteria[45,46] to monitor validity and reliability, and continuous assessment of all data collected. To assess the intra and interobserver variability, an external expert in fetal Doppler will assess ten images of each sonographer, and ten randomized patients of each centre will be scanned by all the sonographers. Scans will be performed by a limited number of experienced and specifically trained sonographers in each centre. Angle correction will be always clearly specified and at we will take least three Doppler measurements per fetus per scan. Sonographers will be blinded to Doppler measurements during the US scan, unless clinical reasons recommended to unmask.

3.7. Statistical analysis

Statistical management will be carried out according to previously described methodology[47] with the objective of establishing prescriptive normal standards for the MCA, UA and CPR Doppler. It is desirable to be able to use all the data from the eight study sites to provide a single global standard for each measurement and to give the strongest basis for the construction of Doppler curves for international clinical applications. However, it is important to be satisfied that the

data from the different centres are similar enough to be combined. The appropriateness of pooling data from all sites to construct UA, MCA and CPR standards will be assessed by comparing site means, standard deviations and the fitted centiles from the analysis of each site to the corresponding values from analyses of data from all sites combined. A difference of > 0.5 SD between the values for an individual site and the pooled sample will be used as a pre-set trigger for considering whether to adjust by site for the purposes of pooling data. We will conduct sensitivity analyses exploring the effect of removing each of the populations in turn on the pooled mean at different gestational ages and the estimated regression models.

We will report the mean and SD of each measurement and sample size for each completed week of gestation. Data will be presented in a scatter diagram Doppler chart including the 5th, 50th and 95th centiles. Reference centiles should change smoothly with gestation, and they should provide a good fit to the raw data. It is desirable for the statistical model to be as simple as compatible with these requirements.[48] Fetal Doppler measures change smoothly and systematically over gestation and have a normal distribution for a given gestational age. We will thus initially apply simpler models, based on fractional polynomial regression functions for the mean and SD of each fetal measurement assuming normality at each gestational age[49], and only move to the more complex models described elsewhere[28] if the fit is inadequate. The distributions of residuals for the fitted centiles for each fetal measurement will be examined both for all sites combined and for each site separately and plotted against the gestational age. The maternal and fetal outcomes will also be analysed through a descriptive analysis in order to describe the sample and exclude those patients in whom an exclusion criterion may appear before or after delivery. Analyses will be performed using STATA software (StataCorp, College Station, Texas, USA) and R version 3.5 (R foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

3.8. Ethics and safety

This protocol has been approved by the ethic committee of Aragon (REF), the research ethics committees of the individual participating institutions and the corresponding regional health authorities in which the project will be implemented. Exposure to ultrasound should comply with the ALARA ('as low as reasonably achievable') principle.[50] The mechanical and the thermal index will be always kept below 1.9 and 1.5 respectively.

No financial compensation will be made to patients who agree to participate. Pregnancy control and delivery assistance will always be attended by experienced personnel, in accordance with international clinical standards. The study will not interfere with any of the centre's care tasks. Information management will always meet with the laws of each one of the involve centres. The fair and dignified treatment of the personal data of every patient included in the study will be guaranteed.

Table 1. Institution selection criteria[26]:

1. Reference hospitals controlling all pregnancies of a health area.
2. Hospitals with a Neonatal intensive care unit.
3. Hospitals with a Fetal medicine unit
4. Located at an altitude below 1600 meters.
5. Perinatal mortality <20/1000 live born.
6. Mothers attending antenatal care in these institutions should plan to deliver in that hospital
7. Lac of known non-microbiological contamination such as pollution, radiation or any other toxic substances

Table 2. Patient selection criteria[26]

2.a. Baseline maternal characteristics

1. Written informed consent for participation in the study
2. Singleton pregnancy
3. Aged ≥18 and <35 years
4. BMI ≥18.5 and <30 kg/m2
5. Height ≥ 153 cm
6. No evidence of socio-economic constraints likely to impede fetal growth identified
    a. using local definitions of social risk

2.b. Personal and gestational history

1. No relevant past medical history, with no need for long-term medication (excluding routine iron, folate, calcium, iodine or multivitamin supplements)
2. No more than one miscarriage in the two previous consecutive pregnancies.
3. No previous baby delivered preterm (<37+0 weeks of gestation) or with a birthweight <2500 g or >4500 g.
4. No previous neonatal or fetal death, previous baby with any congenital malformations, and no evidence in present pregnancy of congenital disease or fetal anomaly.
5. No previous pregnancy affected by pre-eclampsia/eclampsia, HELLP syndrome or a related pregnancy-associated condition.

2.c. Evolution of the pregnancy

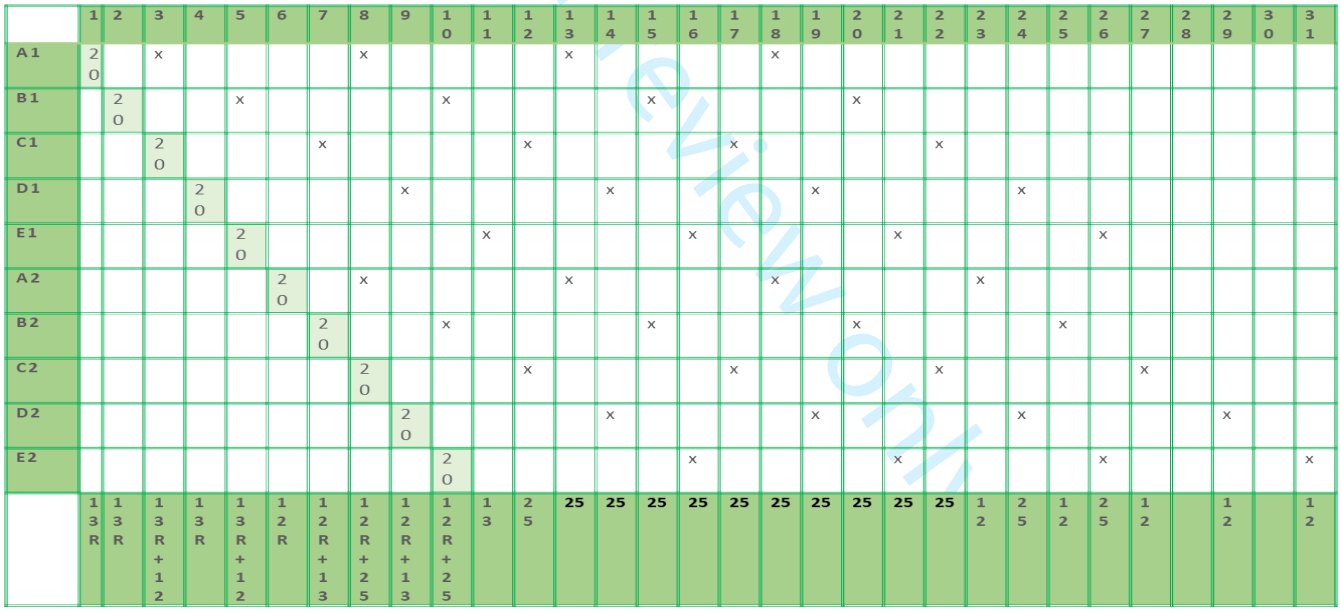
1. Natural conception
2. LMP adjusted by ultrasound with crown–rump length (CRL), between 9 weeks and 0 days and 13 weeks and 6 days
3. Normal second trimester ultrasound scan.

4. No use of tobacco or recreational drugs such as cannabis in the 3 months before
5. becoming pregnant
6. No alcohol use during pregnancy
7. No clinically significant atypical red cell alloantibodies.
8. Systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg.
9. Haemoglobin >10 mg/dl at booking
10. No clinical evidence of any other sexually transmitted diseases.
11. Not in an occupation with risk of exposure to chemicals or toxic substances, or very physically demanding activity to be evaluated by local standards. Women should not be conducting vigorous or contact sports, such as scuba diving or similar activities.

Table 3. Follow up scheme

Weeks of gestation				
A	22	27	32	37
B	23	28	33	38
C	24	29	34	39
D	25	30	35	40
E	26	31	36	41

Figure 1. Example of Follow up protocol for each centre



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NUFFIELD DEPARTMENT OF OBSTETRICS & GYNAECOLOGY

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Spain
31st March 2017

To whom it may concern,

RE Visiting Observership at the Nuffield Department of Obstetrics and Gynaecology

It was a pleasure to host Dr Sara Ruiz Martinez at the Nuffield Department of Obstetrics and Gynaecology in Oxford for her research (1st January- 31st March).

During these three months, Sara Ruiz Martinez focussed her learning in fetal medicine, collaborating with the Fetal Medicine Unit and Ultrasound Department. She contributed to our ongoing studies into fetal growth and health, including a systematic literature review, quality control, data processing and statistical analysis.

Yours sincerely,

Aris T Papageorghiou

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UNIVERSIDAD DE ZARAGOZA
FACULTAD DE MEDICINA
Registro Auxiliar del Registro General
03 MAYO 2017
Nº: MED- 33720
ENTRADA

CERTIFICADO DE ESTANCIA DE INVESTIGACIÓN

El abajo firmante, director del departamento de ..... de la Universidad de Zaragoza o coordinador del programa de doctorado en ..... Medicina ..... de la Universidad de Zaragoza (elíjase una de las dos opciones),

CERTIFICA que

D/D.ª SARA RUIZ MARTINEZ....., procedente de la Universidad de ZARAGOZA..... ha realizado desde el 01-ene-2017.....*(fecha de inicio)* hasta el .31-mar-2017.....*(fecha final)*

una estancia de investigación enmarcada en el desarrollo de su tesis doctoral en el departamento/instituto/centro de JOHN RADCLIFFE HOSPITAL, OXFORD.. (identifíquese lo que proceda).

Y para que así conste, firmo la presente

en Zaragoza, a 31 de MARZO de 2017

	Visto bueno del responsable/tutor Durante la estancia
Fdo.: Angel Lanas Arbeloa ☐ El director del Departamento ☒ El coordinador del programa de doctorado	Fdo.: ARIS T. PAPAGEORGHIOU

Facultad de Medicina Universidad Zaragoza